The
MEDICAL CLINICS
of
NORTH AMERICA

MAY, 1942

CONTRIBUTORS TO THIS NUMBER

Robert C. Batterman, M.D., Assistant in Therapeutics, New York University College of Medicine; Bellevue Hospital.

Ernst P. Boas, M.D., Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University; Mt. Sinai Hospital.

Linn J. Boyd, M.D., F.A.C.P., Professor of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals; Director of Medicine, Metropolitan Hospital.

Aaron Brown, M.D., Assistant Clinical Professor of Medicine, New York University College of Medicine; Bellevue Hospital.

Frederick Robert Brown, M.D., Assistant in Medicine, New York University College of Medicine; Bellevue Hospital.

Nathan W. Chaikin, M.D., Clinical Instructor in Medicine (Gastro-enterology), New York Medical College; Flower and Fifth Avenue Hospitals; Metropolitan Hospital.

Lindsley F. Cocheu, M.D., Professor of Bacteriology, Clinical Pathology and Public Health, New York Medical College; Flower and Fifth Avenue Hospitals; Metropolitan Hospital.

Philip Cohen, M.D., Attending Pediatrist, Beth Israel and Bronx Hospitals.

Arthur C. DeGraff, M.D., F.A.C.P., Professor of Therapeutics and Chief of the Cardiac Clinic, New York University College of Medicine; Bellevue Hospital.

Guilford S. Dudley, M.D., F.A.C.S., Director, Second Surgical Division, Bellevue Hospital.

Frank M. Frankfeldt, M.D., Proctologist, Bronx Hospital.

William Harley Glafke, M.D., Associate Attending Physician in Gastro-enterology, St. Luke's Hospital.

Isidore William Held, M.D., F.A.C.P., Clinical Professor of Medicine, New York University College of Medicine; Beth Israel Hospital.

J. William Hinton, M.D., F.A.C.S., Associate Professor of Clinical Surgery, Post Graduate School of Columbia University; Bellevue Hospital.

Arthur L. Holland, M.D., F.A.C.P., Consulting Physician, Mount Vernon and Horton Memorial (Middletown) Hospitals and New York Infirmary for Women and Children.

Stephen P. Jewett, M.D., Professor and Head of Department of Psychiatry, New York Medical College, Flower and Fifth Avenue Hospitals; Director of Psychiatric Department, Metropolitan Hospital.

CONTRIBUTORS TO THIS NUMBER

Solomon D. Klotz, M.D., Fellow in Internal Medicine, New York Medical College, Flower and Fifth Avenue Hospitals; Metropolitan Hospital.

Michael Lake, M.D., F.A.C.P., Instructor in Medicine, Cornell University Medical College; Associate Physician, Midtown Hospital.

Kurt Lange, M.D., Instructor in Medicine, New York Medical College, Flower and Fifth Avenue Hospitals; Metropolitan Hospital.

Joseph Mandelbaum, M.D., Med.Sc.D., Fellow in Ophthalmology, Long Island College of Medicine; Brooklyn Eye and Ear Hospital.

Thomas H. McGavack, M.D., F.A.C.P., Associate Professor of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals.

Gordon McNeer, M.D., F.A.C.S., Assistant Attending Surgeon, Memorial Hospital.

Brittain Ford Payne, M.D., F.A.C.S., Assistant Clinical Professor of Ophthalmology, New York University–Bellevue Medical School; New York Eye and Ear Infirmary.

McKinnie L. Phelps, M. D., Assistant Visiting Anesthetist, Bellevue Hospital.

H. McLeod Riggins, M.D., F.A.C.P., Associate in Medicine, College of Physicians and Surgeons, Columbia University; Medical Director, Triboro Tuberculosis Hospital.

David Scherf, M.D., Associate Clinical Professor of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals; Chief of Section on Cardiology, Metropolitan Hospital.

John Russell Twiss, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Post Graduate School of Columbia University; New York Post Graduate Hospital.

Roy Upham, M.D., F.A.C.S., Associate Professor of Medicine and Head of Section on Gastro-enterology, New York Medical College, Flower and Fifth Avenue Hospitals.

Robert P. Wallace, M.D., Assistant Clinical Professor of Medicine and Physician-in-Charge of Gastro-intestinal Clinic, New York University College of Medicine; Bellevue Hospital.

Asher Winkelstein, M.D., Associate in Medicine (Gastro-enterology), Columbia University; Chief of the Gastro-intestinal Clinic, Mt. Sinai Hospital.

Frank C. Yeomans, M.D., F.A.C.S., Professor of Proctology, New York Polyclinic Medical School and Hospital.

CONTENTS

CONTENTS

MANAGEMENT OF THE PEPTIC ULCER PATIENT

I. W. HELD, M.D., F.A.C.P.*

It is almost axiomatic that if the medical treatment, and in many instances the surgical treatment, of peptic ulcer is to be successful, it must be directed not only to the local lesion but to the patient himself. It is equally true that supervision of the patient must be continued long after the disappearance of the immediate symptoms. One of the primary reasons for the frequent recurrence of peptic ulcer is that we who treat ulcer patients do not sufficiently impress upon them that dietetic care and the avoidance of excessive strain, worry and excitement must be their rule throughout life if recurrences and serious complications are to be avoided.

With regard to chronic infectious diseases, especially those in which contagion is a factor, the physician, the patient and the community spare no effort to prevent a spread of the disease and cure the afflicted. In part, this is due to fear of contagion and in part to economic necessity. Our great interest in curing diabetes also has in it an economic element. With regard to peptic ulcer, however, which incapacitates almost as many people and is therefore almost as great an economic problem, the general attitude is one of indifference. This situation is deplorable, and is particularly to be regretted at the present time.

One of the most startling revelations of World War I was the fact that the number of soldiers rendered useless by pep-

* Clinical Professor of Medicine, New York University College of Medicine; Attending Physician, Beth Israel Hospital.

tic ulcer exceeded the number disabled by all other affections, and it has since been observed that many men who succeeded in going through the war with a minimum of complaint later became a burden upon society as indicated by Veterans' Hospital records. In World War II, this story is already being repeated. The military hospitals are finding peptic ulcer a major medical problem, second only to psychiatric conditions.

There is little that physicians can do to alter the trying circumstances of the period in which we live, but we can concern ourselves with (1) maintaining the health and wellbeing of those who are predisposed to peptic ulcer, and (2) so managing the patient and his ulcer that such dread complications as perforation, hemorrhage, stenosis and carcinomatous degeneration will occur in minimal degree.

PROPHYLAXIS

The first step in prophylaxis is to realize that, according to most authorities today, peptic ulcer is a local disease on a constitutional basis, and that underlying both is an instability of the autonomic nervous system which disposes the individual to react abnormally to all stimuli.

The constitutional factor may be:

(1) *Congenital*. Draper has eloquently described the individual with a congenital gastric ulcer status as a "lantern-jawed, hungry-looking person with a nervous, introspective and sensitive temperament," and the individual with a congenital duodenal ulcer status as broad-jawed and plethoric;

(2) *Conditioned constitutional*. Individuals with a conditioned constitutional defect fall into two groups:

(*a*) Persons normal at birth and who continue to be so until, for some reason, they become "stomach conscious" and begin to eliminate one article of food after another from their diet and so develop a hypotonic or an atonic and ptosed stomach, and even duodenum, leading to gastric stagnation, hypersecretion, hyperacidity, and possibly to gastric ulcer. Extreme dieting in order to reduce weight is the result of a social trend to make the body fit the dress, and not the dress fit the body. It is partly, also, the fault of the medical

profession for approving and even publicizing the idea that weight and height must have certain proportions in order to be normal. Not the least harmful factor of weight reducing is the fact that the vitamins lost with diminished food intake cannot be adequately replaced by "pills";

(b) Persons of normal habitus at birth who in adult life—often at the very age when weight increase is naturally to be expected—begin to consume excessive amounts of food in order to gain weight, and so convert the stomach from an orthotonic to a hypertonic organ, bringing about too rapid emptying of the gastric contents into the duodenum, and possibly a duodenal ulcer.

Every attempt should be made to influence these individuals to return to a normal diet.

If the trade or occupation of the individual predisposed to peptic ulcer subjects him to great stress and faulty eating habits, he must be urged to find a less exacting means of livelihood, being told frankly that if he does not do so and if he does not face his daily tasks calmly, he runs the risk of developing a very serious illness. For the same reason, those who overeat must be cautioned against artificially developing a secondary plethoric habitus.

Individuals who are extremely neurotic should be encouraged to undergo actual psychoneurotic training.

SIMPLE PEPTIC ULCER

In spite of all that physician and patient can do to prevent it, many individuals will develop a peptic ulcer, which fortunately in the majority of cases is a simple ulcer amenable to medical therapy.

By simple ulcer we mean a lesion with typical symptoms but one in which a most careful physical examination, including roentgenography, reveals neither a delay in the emptying time of the stomach nor any other specific evidence of ulcer with the possible exception of a minute niche at the site of the lesion.

If, in spite of meager physical signs, we are convinced that the patient's symptoms are due to peptic ulcer, treatment should be begun at once and should be carried out as

rigidly as though the physical findings had been amply confirmatory.

The patient should go to bed and stay there for at least a week, during which time he is to be protected from all mental worry and anxiety. This protection should be continued for at least three or four weeks after he is out of bed. At the very outset, he should be taught not only what to eat but *how* to eat. He must eat slowly, not partake of anything too hot or too cold, and even liquids should not be gulped.

Dietetic Regimen

During the first seven to ten days, when the patient is confined to bed, his diet is to be so regulated as to prevent, insofar as possible, the occurrence of periodic pain. This is best accomplished by putting the patient on the Sippy diet, or some modification thereof. The modification that we have found most useful is the following:

FIRST THREE DAYS: The patient is fed milk, not every hour as in the Sippy diet, but every two hours, throughout the twenty-four-hour period unless he sleeps through the night. At each feeding he is given 10 to 12 ounces of milk with 3 ounces of sweet cream. If after two hours no hunger pain or discomfort occurs, the interval between feedings may be increased gradually to three hours.

Patients are occasionally encountered who do not tolerate milk well. If the milk causes distention or diarrhea, it should be diluted with barley water—half milk, half barley water. This water is prepared by cooking barley for one and one-half hours in water to which a little salt has been added for seasoning. If the diarrhea persists, rice cooked for two hours in a double boiler served with milk and sweet cream may be substituted.

NEXT FOUR DAYS: If the acute symptoms have subsided, the patient is given on the *fourth day* every three hours: 6 ounces of milk, 2 ounces of sweet cream, and one soft boiled egg. By the fifth day he is usually tired of milk; even an egg is not sufficient variety. Therefore, his meals on the *fifth, sixth and seventh days* are as follows:

1st feeding:	6 oz. milk, 2 oz. sweet cream. 1 soft boiled egg
2nd " :	Cereal—preferably hominy (the most easily digested cereal) cooked in milk for 15 minutes in a double boiler and served with butter, 10 oz. of milk and 1 oz. sweet cream
3rd " :	6 oz. milk, 2 oz. sweet cream, 1 soft boiled egg
4th " :	6 oz. milk, 2 oz. sweet cream, and the same amount of cereal prepared as at the second feeding

Before sleeping: 10 to 12 oz. milk, 3 oz. sweet cream

Drip Method of Feeding.—Winkelstein[1] has recommended feeding the *milk* during the first week (longer, if indicated) through a duodenal tube left in situ during the night. This is particularly beneficial when the patient has a duodenal ulcer because in this lesion the acid secretory function is as active at night as during the day. The dripping milk binds the secretions and permits the patient to sleep. This method of feeding may bring about a complete remission of symptoms within a week or two.

Woldman and Rowland[2] instead of giving the milk by the drip method prefer to give the patient an *aluminum hydroxide mixture* by drip. This is prepared as follows: 7 per cent colloidal suspension of aluminum hydroxide is well mixed in distilled water in the ratio of one-third aluminum hydroxide to two-thirds water. This is administered by the drip method through a small Levin tube (size 12) until 1600 cc. have entered the patient's stomach. This is done once or twice a day for twelve to fourteen days. In addition, the patient is put on the regular Sippy diet regimen.

SECOND WEEK: Beginning with the second week, and in some cases during the latter part of the first week, the patient is allowed bathroom privileges and may even take a bath not only for cleanliness but for morale. He may also enjoy company but must be protected from anxiety and mental strain. The feeding interval is increased to four hours and the meals are as follows:

Breakfast:	Cereal—hominy or some other cereal
	(If oatmeal is chosen, it should be cooked in milk in a double boiler for 1 to 1½ hours; if rice, it should be cooked in milk in a double boiler for 2 hours; if a dry cereal is preferred, then corn flakes are best because of their high vitamin B content)

	2 soft boiled eggs 10 oz. milk, 1 oz. sweet cream 1 slice buttered white toast
Lunch:	White of chicken cut into fine pieces Mashed potatoes and butter 1 slice buttered white toast 10 oz. milk, 1 .oz. sweet cream
Midafternoon:	10 oz. milk, 2 oz. sweet cream 2 or 3 Graham crackers (nourishing and vitamin-rich)
Dinner (7 or 7.30 P.M.):	Boiled fish Mashed potatoes Apple sauce with cream 6 oz. milk
On retiring:	10–12 oz. milk 2–3 Graham crackers

THIRD WEEK: Meals every five hours, as follows:

Breakfast:	Milk or cocoa cooked in and served with milk, *or* Ovaltine with milk, *or* Moderately strong caffeine-free coffee 2 eggs Cereal
Lunch:	Any kind of finely cut meat, except fried Mashed potatoes with butter Custard or rice pudding Glass of milk
Midafternoon:	Glass of milk Few Graham crackers with butter
Dinner (7 or 7.30 P.M.):	Small piece of ripe honey-dew melon, *or* Small glass of sweetened orange juice Some form of meat, cut fine Rice pudding and milk Pear compote or apple sauce with cream
On retiring:	Another glass of milk

Whether the patient is to drink orange juice, so rich in vitamin C, is entirely dependent upon the symptomatic reaction of the patient. If the orange juice is taken on a fasting stomach it may cause pyrosis. There is no harm in keeping the patient away from orange juice for the first two weeks.

FOURTH WEEK: Three meals a day as follows:

Breakfast: Baked apple and sweet cream
2 poached or soft boiled eggs
Cereal
Buttered white toast
Milk, cocoa or caffeine-free coffee

Lunch: Small glass of orange juice, *or*
Some ripe fruit pared and scraped
Cream or pot cheese
Baked potato with butter
White meat

4 P.M. Glass of milk
Buttered toast *or* Graham crackers

Dinner: Glass of milk
Small quantity of barley soup (avoiding chicken and meat
soups)
String beans, lima beans, peas or carrots (no spinach, which in-
creases gastric secretion)
Fruit compote: preferably cooked pears, apples or prunes

FIFTH WEEK: Same as fourth week.

SIXTH WEEK: The patient may now be allowed more raw fruit, *or* grape juice, *or* orange juice. Food as for the fourth week, *avoiding all spiced foods and condiments*.

AFTER THE SIXTH WEEK: Every ten days to two weeks, the patient should remain in bed for a day, eating only milk, sweet cream, eggs and cereal. This will be helpful in preventing a relapse, and this regimen should be carried out until the patient feels entirely well. It should be repeated every spring and fall, when the bed rest period should be extended for a week, if possible, the meals consisting of milk, sweet cream, eggs and cereals as in the first week of treatment outlined previously.

Smoking.—There is no question whatsoever that smoking is a hindrance to healing. The acidity of the gastric contents of patients with peptic ulcer after smoking has been proved in some instances to be twice that of the acidity before smoking.[3] Therefore, every effort must be made to persuade the patient to desist. As a rule, absolute proof that smoking is injurious will suffice to bring this about.

Medication

The aim of medication in the treatment of a simple ulcer is to overcome pylorospasm and hyperacidity. Although we do not subscribe to the theory that hyperacidity is directly responsible for ulceration, we readily admit that it can change the pathologic character of an existing ulcer and in this way prevent healing and even convert a simple ulcer into a complicated one.

Gastric Lavage.—As a means of eliminating hyperacidity, Sippy advocated washing out the stomach night and morning. We have never found this necessary when pyrosis is not the dominant symptoms.

Alkalies.—Sippy also advocated massive alkalinization every hour: sodium bicarbonate, calcium carbonate, bismuth subcarbonate and magnesium oxide. This, too, we have not found necessary. In reality, overalkalinization causes the persistence or the recurrence of symptoms and produces painful urination in both men and women. In the middle-aged male with a diseased prostate, overalkalinization may initiate or intensify prostatic symptoms and may even cause acute urinary retention and renal damage.

Alkalies should be given only when the dietetic regimen and ample rest are ineffective in relieving symptoms. Then the alkalies should be given in *small doses:* for example, 0.65 gm. trisilicate alone; or a combination of 0.32 gm. calcium carbonate, 0.32 gm. calcium phosphate, 0.32 gm. magnesium trisilicate, and 0.32 gm. magnesium oxide, *in half a glass of water, sipped slowly, fifteen to twenty minutes after each feeding.*

Antispasmodics.—If required, tincture of belladonna, 10 drops twice a day, may be given one hour before meals or one of the newer preparations like trasentin (Ciba) or syntropan (Roche) in tablet form, one hour before meals.

Olive oil, 1 or 2 tablespoonfuls in the morning and 1 tablespoonful before retiring, is very effective. Olive oil treatment is based on the fact that fat causes bile and intestinal secretions to regurgitate in the stomach, thus diminishing and neutralizing existing gastric secretions. This was first experimentally demonstrated by Ewald and Boas[4] in 1883. In 1926,

Farrell and Ivy[5] showed conclusively that fats, particularly light cream, milk and butter, can inhibit the motility of a transplanted gastric pouch. In 1934, Quigley, Zettleman and Ivy[6] demonstrated that it does so only when in the intestines.

Enterogastrone.—Ivy and his co-workers[7, 8] have shown that the parenteral injection of an extract of the intestines of animals that had been kept on a fat diet is effective in reducing gastric secretion, and have called the extract "enterogastrone."

Urogastrone.—Friedman, Rechnagel, Sandweiss and Patterson,[9] following this same line of experimentation, obtained from the urine of pregnant female animals and from the urine of normal female animals and of some male animals, an extract which, when injected intramuscularly or intravenously, inhibited gastric secretion. Sandweiss, Sugarman, Friedman, Saltzstein and Farbmann[10] confirmed this experiment and went on to show that (1) when applied to dogs it can prevent the formation of Mann-Williamson ulcers, and (2) when applied to the human, gastric secretions are inhibited. These findings are of great promise, first of all because they demonstrate that fat acts as an inhibitor of gastric secretion by its humeral influence, and, secondly, because one of the important causes of peptic ulcer may be a disturbance in the humeral factors responsible for enterogastrone and urogastrone so that gastric secretion becomes excessive.

Gelatin.—2 or 3 tablespoonfuls of some gelatin preparation after each meal have been found helpful in reducing acidity.[12]

Mucin.—Following reports by Jacob Kaufmann that the presence of mucus in the stomach is of great importance in neutralizing acidity, efforts were made to encourage this medically. Ivy succeeded in producing a substance which he called mucin. In some cases this has relieved symptoms due to hyperacidity.

ATYPICAL SIMPLE PEPTIC ULCER

There are many cases of simple peptic ulcer in which *pyrosis* is the only symptom, but a very troublesome one. Roentgen examination reveals, at most, evidence of duodenal irritability. These patients tire soon of dieting and of their

physician. They resort for relief to proprietary drugs and begin to consume large amounts of alkali, usually bicarbonate of soda. The overalkalinization that results not only adds to the irritation of the gastro-intestinal tract, but may actually produce mild alkalosis, gastric catarrh, and even a severe gastric hemorrhage. For this reason, the symptom of pyrosis must be treated with unusual patience and care.

Tobacco and liquor must be absolutely interdicted. Meals must be eaten slowly, at regular intervals.

Alkalies.—It is far better for the patient to endure his pyrosis than to attempt to cure it by overalkalinization. Alkalies should not be taken in greater quantity than outlined

Duodenal Alimentation

First to third days:	1 glass warm milk and 1 tablespoonful of glucose every 2 hours
Fourth and fifth days:	Add yolk of egg to milk 3 times daily
Sixth day:	Add yolk of egg to each feeding
Seventh day:	Add entire egg to three feedings
Eighth day:	Add entire egg to every feeding
Ninth day:	One tablespoonful sweet cream is to be added to every feeding
Tenth and eleventh days:	Add 2 oz. orange juice sweetened with 2 teaspoonfuls of sugar twice, between feedings
Twelfth to fourteen days:	Add 1 tablespoonful sweet cream to each feeding, and orange juice (4 oz.) with sugar 3 times a day, between feedings
After the fourteenth day:	The diet should be as outlined above for patients having a typical simple ulcer

previously. In some cases, *magmasil* may be included or substituted. Silverman and Katz[13] have recently recommended it in cases with particularly severe hypersecretion symptoms. Two teaspoonfuls should be given every hour during the period of acute symptoms. Magmasil contains 20 per cent hydrated active magnesium trisilicate in aqueous suspension.*

Gastric Lavage.—The most helpful measure at our command is gastric lavage. Indeed, it is almost indispensable because the gastric contents of the fasting stomach of these patients almost always reveal a microscopic and even macro-

* Boyd, L. J. and Barowsky, H. advocate the use of a special preparation, Aluminoid, which we find very effective (Rev. of Gastroenterology. 9: No. 1, pp. 20-25, Jan.-Feb., 1942).

scopic residue. The lavage of the fasting stomach should be done with 1 pint of mild alkaline solution every morning for seven to ten days. In some cases it is necessary to lavage the stomach twice a week for several months.

Syntrogel in capsule or emulsion form may be helpful.

Antispasmodics should be given when indicated, as described above. Olive oil is particularly valuable, a tablespoonful night and morning.

Bed Rest and Diet.—When pyrosis is extremely troublesome, the patient should be kept in bed, completely at rest for two weeks and should be fed through the Einhorn duodenal tube (see p. 654).

PEPTIC ULCER EVIDENCED BY A NICHE

In many cases, roentgenologic examination will reveal a niche, usually on the lesser curvature of the stomach or in the first portion of the duodenum, indicating the presence of a large ulcer. In most of these cases, due to chronicity, there is also evidence of pylorospasm, loss of gastric tone, and delayed emptying time. In view of these findings, it would seem that medical treatment would be a waste of time, but the fact is that in the majority of cases it will be as successful as in the treatment of simple ulcer. The only difference is that the dietetic regimen must be more strictly carried out and for a longer period of time. The milk and sweet cream diet should be continued until the pain has disappeared. Then solid food may be permitted but only gradually, in amounts that will not cause the symptoms to recur. Should the patient experience the slightest discomfort, the milk diet should be resumed for a day or two. Under such a regimen and with medication as outlined above, the niche may disappear entirely.

Disappearance of a niche, however, does not mean that complications may not occur. Although a scar may form, seeming to indicate that healing is complete, nevertheless a localized area of erosion may remain in which ulceration can occur, and even hemorrhage or perforation. In some cases, the original niche has come back after months or years. However, once it disappears the niche usually does not recur.

The niche of a gastric ulcer disappears more often than does one of a duodenal ulcer. This is due probably to the fact that the duodenum, particularly the first portion, is so thin-walled that protrusion at the site of the ulcer occurs with only a slight degree of intraduodenal pressure. The presence of a niche in the duodenum, therefore, does not of necessity indicate great ulcer activity. A deformity of the duodenum due to spasm is sometimes manifested in the x-ray film as a clover leaf, or goose feather, with an eccentrically located pyloric canal; the deformity may disappear and the niche remain. A pseudodiverticulum of the first portion of the duodenum may also disappear, with a niche remaining. This is true, too, of a niche on the greater curvature of the duodenum in the case of an ulcer associated with periduodenal adhesions; the niche may be present long after all symptoms have disappeared.

In all of these cases, regardless of the niche, strict medical care may bring about the prolonged relief of the patient's symptoms and even the permanent cure of the ulcer.

A large niche in itself does not imply the presence of an active ulcer. Should, however, symptoms continue under medical treatment, should atony of the stomach become more marked, or should the niche increase in size in spite of treatment then the patient should be given the benefit of *surgery*. This is indicated as much for the relief of the symptoms as it is for the possibility of a *cancerous degeneration* of the ulcer.

Aschoff does not believe that an ulcer ever becomes cancerous; he feels that if there is a cancer it started as one and not as an ulcer. Lahey, until recently, was inclined to agree with this view, but since employing the gastroscope has come to regard some cancers as possibly the result of a degenerative process in an ulcer. Schindler, on the other hand, has concluded (personal communication) from his very extensive gastroscopic studies that cancer never occurs on the basis of a peptic ulcer.

We are not willing, from our experience, to agree entirely with Schindler. Neither would we concur wholly with the late Carman who looked upon any niche larger than 2.5 cm. as a potential cancer. We do not believe we have seen a case

that has become a cancer on the basis of ulcer, even in patients who have suffered from ulcer symptoms for more than thirty-five years. However, it is the part of prudence to resort to surgery when symptoms do not improve, and particularly when an already large niche gives the slightest indication of increasing in size in spite of medical treatment.

PEPTIC ULCER COMPLICATED BY STENOSIS

We come now to the treatment of cases which develop a first, second or third degree of stenosis due to a niche and adhesions, or deformity of the pylorus as the result of an ulcer near the pylorus, with associated atony of the stomach, or a deformity of the duodenum as a result of ulcer and associated spasm of the pylorus and sphincter pylori.

Patients with advanced stenosis who are still in the prime of life will be far happier to undergo a *subtotal gastrectomy* than to be kept on medical treatment almost constantly with suffering not always relieved, and generally weakened by secondary anemia and avitaminosis. If, however, the patient declines operative relief or cannot have it because of some associated condition such as hypertension or chronic emphysema, then we must do our best to keep the symptoms alleviated over a long period of years.

If surgery is decided upon, the operative procedure should be preceded by gastric lavage for several days, intravenous saline with glucose, and injections of vitamins B and C.

If medical treatment is undertaken, *gastric lavage* is our best ally. If the patient has a twenty-four-hour residue, the stomach should be lavaged every night for one week three hours after the last meal, and in the morning before the first meal. This lavage may be done with normal saline solution, or with mild alkaline. We prefer the former which avoids the risk of hypochloremia or alkalosis. For the second week, nightly lavage should be sufficient. During the third week "dry extraction," using the Ewald tube, should be carried out. Dry lavage has the advantage of acting as a gastric massage to increase the tone of the stomach. The atony and spasm should be relieved by the end of three weeks, and roentgen examination then should show that the stomach is

emptying within normal time, provided the diet is one that does not overtax the stomach.

The *food* eaten should be high in qualitative and not in quantitative value: milk, cream, cereals, and other nourishing items for the first two weeks, with orange juice or grapefruit juice and other vitamin-rich foods added at the beginning of the third week. Following this, the patient must not forget that he is a gastric invalid and must adhere strictly to food along the lines indicated in the treatment of simple peptic ulcer. He must also lead a physical and mental life compatible with his disease. By doing so, he may be very comfortable for months and even years.

HEMORRHAGE DUE TO PEPTIC ULCER

The first principle in the treatment of gastric hemorrhage is *absolute rest of body and mind*. When a man or woman suddenly realizes that he or she is losing blood from an internal organ, the shock is not only immediate but lasting. The patient's mental unrest must be controlled if treatment is to be effective. Therefore, the first requisite is for the physician to maintain an extremely calm attitude when in the presence of the patient. Here, more than in any other condition, he must, in the words of Oliver Wendell Holmes,

> "—And last, not least, in each perplexing case,
> Learn the sweet magic of a cheerful face."

Measures for Immediate Relief

Sedatives.—The first medical aid is *morphine sulfate* 0.015 gm. hypodermically; no other drug so quickly relieves anxiety and calms the mind. If this is not effective, or if it causes nausea, then *pantopon, papaverine* or *perparine* (0.02 gm.) may be given intramuscularly. In order to keep the patient quiet and euphoric for several days, the drug is repeated every three or four hours, depending upon the patient's condition. Although pharmacologically these drugs are identical with morphine (with the experimental pharmacologist mildly condemning their use as substitutes), they produce a soothing effect without causing the pylorospasm and vomiting induced in some patients by morphine. Some clinicians advise, for patients who vomit a great deal of blood and are exceptionally

restless, morphine sulfate or codeine sulfate intravenously, one-third the dose that would be given hypodermically.

If morphine or one of its substitutes has no effect on restlessness, the patient should be given *sodium amytal* (isoamylethylbarbituric acid) intravenously (0.3 gm.), or *chloral hydrate* (1 to 1.5 gm.) with *calcium bromide* (5.0 gm.) in 50 cc. of lukewarm physiologic salt solution, by rectum to be retained. This may be done, without disturbing the patient, through a shortened syringe into the rectum with the patient lying on his back, buttocks slightly elevated. In exceedingly restless cases, add tinctura opii 2 cc. to the chloral hydrate. Coagulose and thromboplastin have been advocated by some authors, but we have not seen any beneficial results from their employment.

Gastric Lavage.—Should the vomiting of blood continue and assume the form of large clots, it may be necessary to lavage the stomach either with ice water or hot water, 102°–104° F. This may seem like heroic treatment, but clots in the stomach act as foreign bodies to prevent its contraction. By removing them, we enable the stomach to contract upon itself and so aid in stopping the bleeding. Some authors advocate adding adrenalin hydrochloride (1:1000, 1 to 2 cc.) to the lavage solution.

Intravenous Therapy.—Another remedy is the intravenous administration of hypertonic sterile solution of *sodium chloride*, 5 to 10 cc.; *calcium gluconate* (20 to 50 cc. of 5 per cent solution); or *calcium chloride* (10–20 cc. of 5 per cent solution). If calcium chloride solution is used, one must be certain to enter the vein without losing the tiniest drop of solution into the surrounding tissue; otherwise severe inflammation, even necrosis, may occur.

Cold to Abdomen.—The application of cold to the abdomen—in the form of cold water passing through a coil, an ice bag, or a towel made cold by running water—has a very soothing effect.

Treatment of Shock and Syncope.—If shock is marked, an important measure is immediately to bandage the arms and legs to the extent of obliterating the veins, but not the arteries, thus preventing the return of venous flow. When

there is a tendency to syncope, elevation of the foot of the bed for twenty-four to forty-eight hours is helpful. It is essential, also, to give glucose enemas, and, if possible, hypodermoclysis, preferably of Ringer's rather than saline solution which increases thirst.

Vasomotor and Cardiac Stimulants.—Vasomotor stimulants like camphor in oil (0.45 gm. intramuscularly), strychnine sulfate (0.002 gm.), and caffeine sodium benzoate (0.3 gm.) may have to be administered. If so, they should be given alternately at hourly intervals until the patient rallies. Ergotin (0.006 gm.) intramuscularly is also advocated on the basis of being a cardiac stimulant. It must be remembered, however, that these drugs are to be given only when all other means of treatment have proved futile and evidence of peripheral failure is present.

Glucose Administration.—If dehydration continues to be marked, an increased amount of glucose should be given by the Murphy drip method, 20 per cent in 200 cc. twice daily.

If the pulse remains weak and the blood pressure is low, glucose should be administered intravenously within three to six hours, 50 cc. of 10 to 20 per cent solution. Occasionally, this is followed by a rise in temperature but this is temporary and has no ill effect.

Blood Transfusion

There has been some controversy regarding whether blood transfusion should be given early in hemorrhage. Some clinicians advise against it out of fear of raising the blood pressure and hence increasing the bleeding. But this has certainly not been our experience. In fact, *if hemorrhage is severe,* we believe that *a blood transfusion should be administered as soon as possible.* Anyone who has watched the effect of a blood transfusion in cases of grave bleeding from internal organs and has seen color return to the face, and the restlessness quickly disappear, must surely admit the value of such treatment. Blood transfusion has the advantage, also, of introducing to the circulation a colloid that stays there and fills the blood vessels, thus preventing peripheral failure. It has a further merit in that it replaces proteins and is a hemostatic.

The first transfusion should not be more than 500 cc., although we have seen 750 cc. given with excellent results. If the hemorrhage has not ceased within twenty-four to forty-eight hours, or if the symptoms of collapse continue to be marked, a second transfusion is indicated; only in this way can life be saved in the most desperate cases.

Should it be impossible to give an immediate blood transfusion, it is advisable to try Starling's solution.

Care of the Mouth

Owing to the loss of fluid from the body and the fact that the patient takes almost nothing by mouth for some time, extreme dryness of the mouth develops and may cause stomatitis and parotitis., leading to an abscess of the parotid gland. Such complications are due solely to poor mouth hygiene. If dryness cannot be overcome by rinsing the mouth with water, or by keeping ice in the mouth, chewing gum will be helpful in stimulating salivary secretions. Although gum also stimulates gastric secretion, it is a risk that must be taken; otherwise, fatal sepsis may develop.

Length of Time in Bed

One month is the minimum for bed treatment, and it should be six weeks. The patient should not be permitted to sit up until occult blood has disappeared. Sitting up, then, should be a gradual process during which the blood pressure is watched. Low blood pressure is advantageous because it favors cessation of bleeding, but if it remains below 100 mm. of mercury systolic after occult blood has disappeared it may be due to persistent vasomotor paresis, so that if the patient sits up too suddenly he may collapse. Strychnine sulfate (0.002 gm.), ephedrine sulfate (0.05 gm.), or pituitary extract (0.06 gm.) three times a day by mouth, given three or four days before sitting up, will stabilize the vasomotor system and increase blood pressure.

Feeding

Andresen and Meulengracht Diets.—In 1927, Andresen[14] recommended the administration of a gelatin water mixture

at two-hour intervals to the patient with gastric hemorrhage *on the first day*. Other nutriments were to be added on the second and third days. His justification for this previously unheard-of procedure was the fact that the stomach is less active when full than when empty. Within a short time, Meulengracht[15] began feeding the patient from the very onset of hemorrhage, giving on the second day a puréed high calorie, high vitamin diet, and observed that the patients felt better with a full diet. Those who were extremely exsanguinated received one or more blood transfusions. Of 368 cases of liberal feeding reported by Meulengracht, in only one did perforation occur. In 1940, Chasnoff, Leibowitz and Schwartz[16] reported twenty-one cases treated with the Meulengracht diet in Beth Israel Hospital. There were two perforations, but these were in elderly people at the arteriosclerotic age.

The writer has not yet been heroic enough to give a liberal diet to a patient with a bleeding peptic ulcer. However, in the case of patients under forty, even under fifty, we are willing to advance the diet more rapidly, beginning with the sixth day, than we are when the patient is above this age. Then, the Meulengracht diet should not be employed at all. The very young patient may have a more liberal diet (finely chopped meat and vegetables), depending upon his condition, after the second day.

Nutritive Enemas.—It is our practice, so long as there is active bleeding, evidenced either by vomiting of blood or by a tarry stool, to permit no mouth feeding. Glucose should be administered at body temperature by rectum, 100 cc. 20–50 per cent solution, three or four times daily, preceded by a low, cleansing enema. The enema should be warm enough to produce a slight hyperemia in the rectum which will aid in the absorption of the glucose. Although some clinicians believe that glucose administered by rectum is not utilized by the body as food, others contend that 30–40 per cent is absorbed and utilized as food. Tinctura opii (2 cc.) may be added to the solution to aid in retention and to allay the discomfort caused by enteroclysis. Other nutritive enemas such as of milk and eggs are not only valueless but may have an

irritating effect on the bowel. Smithies has advocated 200 to 250 cc. of normal salt solution containing 30 cc. of glucose solution and 30 cc. of 50 per cent alcohol, to be injected at body temperature by the Murphy drip method four times in twenty-four hours.

Early Milk Diet.—As soon as the stool begins to improve in color, indicating the cessation of active bleeding, feeding by mouth may be started. This is generally on the fourth or fifth day after visible hemorrhage.

Small quantities of milk (not more than 2 ounces at a time) to which two teaspoonfuls of limewater have been added, should be given hourly or every two hours. Some patients, however, do not tolerate milk every hour. They should be given milk alternating with carbohydrates, consisting of strained barley with butter or strained oatmeal with sweet cream. It is advisable to give the patient 200 to 250 gm. of sugar in 8 or 10 ounces of water every two or three hours, which has the effect of stimulating water secretion in the stomach, thereby neutralizing the acid without stimulating gastric secretion and gastric peristalsis. Sugar may be added to the milk.

Additions to Milk Diet.—When occult blood has disappeared entirely, more liberal feeding may be begun. Home-prepared gelatin or commercial "jello," of nonstimulating flavor (such as chocolate or vanilla) may be given twice daily. As soon as the patient has tolerated milk and carbohydrates for four or five days, a modified Sippy diet is to be instituted. Feeding at two-hour intervals is ordinarily sufficient, and for this we prefer larger quantities than advocated by Sippy, namely, 8 ounces of lukewarm or cold milk every two hours. After five or six milk days, the interval between the food intake as well as the amount of food is increased. The following regimen should be carried out:

First week after exclusive milk diet:

Every three hours:
- 1 glass warm milk
- 2 tablespoonfuls sweet cream
- 1 slice buttered toast
- 1 soft boiled egg

Second week after exclusive milk diet:	Add to the above:
	Baked or mashed potatoes
	Baked apple with sweet cream, or apple sauce
	Lettuce with olive oil
	Banana with sweet cream
	Cereals (farina, hominy or strained oatmeal)

Third and fourth weeks after exclusive milk diet:	Add to above:
	Dry cereals—corn flakes or puffed rice
	Asparagus tips
	Cauliflower
	Peas
	String beans
	Lamb chops
	Squab
	Stewed prunes with sweet cream
	Hot chocolate or Postum
	Zwieback with butter
	Home-made sponge cake 1 or 2 days old

Fifth and sixth weeks " " " "	Add to above:
	Rye bread 2 days old
	Veal steak, well done
	Calves' brains
	Ice cream

Seventh and eighth weeks " " " "	Add to above:
	Ripe fruit in moderation
	Light coffee

Jejunal Feeding and Postjejunal Diet

If occult blood persists in any degree and if the patient experiences distress in the upper abdomen, even when only milk is consumed, it is best to resort to duodenal feeding, as first advocated by Einhorn, or to jejunal feeding. We prefer to pass the tube into the jejunum due to the fact that with duodenal feeding the duodenum not infrequently becomes overdistended, causing nausea and regurgitation with vomiting out of the tube. This does not happen with jejunal feed-

ing. It has been our experience, too, that gastric acidity persists with duodenal feeding but is diminished with jejunal feeding.

It is essential to adhere specifically to the diet which follows so that almost no weight will be lost during the period that jejunal feeding is continued. After the tube is removed, the patient is kept on milk, sweet cream and soft boiled eggs for four or five days.

Jejunal Feeding

Before introducing any food, blow through the lumen of the tube to see if it is patent; aspirate intestinal contents.

Food is to be introduced through the glass funnel slowly—requiring at least ten minutes.

Total Daily Calories

First day Second day Third day }	250 cc. (1 glass) warm milk, 15 gm. (1 tablespoonful) glucose every two hours	1528
Fourth day Fifth day }	Add yolk of egg to milk, three times a day	1702
Sixth day:	Add yolk of egg to each feeding	1934
Seventh day:	Add entire egg to three feedings	1953
Eighth day:	Add entire egg to each feeding	2053
Ninth day:	Add 1 tablespoonful sweet cream to each feeding .	2350
Tenth day Eleventh day }	Add orange juice, 2 oz., with 2 teaspoonfuls sugar between feedings, twice	2490
Twelfth day Thirteenth day Fourteenth day }	Add 1 tablespoonful sweet cream to each feeding, add orange juice (4 oz.) with sugar (4 teaspoonfuls), three times a day	2770

Note: If cream causes diarrhea, add 0.5 gm. Pankreon to each tablespoonful of cream. The deeper the tube (125 cm.) the less unpleasant the effects. Fifty cc. of water before each feeding will cleanse the tube and alleviate thirst—total 350 cc.

Rinsing of the mouth and cleansing of the teeth several times a day will overcome thirst. Use Dobell's solution or some other mouth wash.

Postjejunal Diet

First day
Second day
Third day } 1 glass of milk with 1 tablespoonful of sweet cream every two hours, beginning at 7 A.M., concluding at 9 P.M. Add 1 soft boiled egg to every other feeding, that is, at 9 A.M., 1 P.M. and 5 P.M.

Orange juice, half glass

Toast and butter

Fourth day ⎫ 1 glass of milk with 1 tablespoonful of sweet cream every
Fifth day ⎬   three hours, beginning at 7 A.M., concluding at 10 P.M.
Sixth day ⎭ Oatmeal—boiled 1 to 1½ hours in a double boiler
             Rice—boiled 1 hour in double boiler
             Toast and butter
             Orange juice
                 The cereal is given every 3 hours with milk and sweet
                     cream to alternate with toast, butter and 1 egg

Example:
    7 A.M.: 1 glass of milk, with sweet cream and cereal
    10 A.M.: 1 " " " toast and egg
    1 P.M.: 1 " " " cereal and egg
    4 P.M.: 1 " " " toast and egg
    7 P.M.: 1 " " " cereal and egg
    9 P.M.: 1 " " " and toast

Seventh day ⎫ Add to above: Baked apple with sweet cream, *or*
Eighth day ⎬   Banana with sweet cream
Ninth day   ⎭   Baked, *or*
                             Mashed potato

Example:
    7 A.M.: Milk and cereal
    10 A.M.: Milk, toast, egg and baked apple
    1 P.M.: Milk, cereal, and baked or mashed potato
    4 P.M.: Milk, toast, egg, and banana with sweet cream
    7 P.M.: Milk, cereal, egg and toast
    9 P.M.: Milk and toast

Tenth day: Meals every four hours

Example:
    8 A.M.: Orange juice, cooked cereal, egg, toast and butter,
        milk
    12 M.: Chicken or boiled fish, potato, toast and butter,
        milk
    4 P.M.: Stewed prunes, banana or baked apple with cream,
        milk, egg and toast
    8 P.M.: Milk and toast

Medication after Active Hemorrhage Ceases

Occasionally, tarry stools will persist beyond the third, fourth or fifth day after the initial hemorrhage so that mouth or jejunal feeding may have to be commenced while some bleeding is still going on. In these cases, medication by mouth may be of great service, as follows:

Alkalies.—If the patient suffers from pyrosis, small doses of alkalies by mouth should be given, preferably a mild alkaline Vichy, a wineglassful after each feeding. If this does not

suffice, add to the Vichy any one of the four alkalies: sodium bicarbonate, calcium carbonate, bismuth subcarbonate, or magnesium carbonate. Sodium bicarbonate has the advantage of facilitating the expulsion of carbon dioxide from the stomach, thus relieving gastric distention. Clinical experience has shown that when a patient takes bicarbonate of soda by mouth he belches almost at once. If he takes calcium carbonate this phenomenon does not take place, thus it may be assumed that calcium carbonate does not give off carbonic acid as readily in the stomach as does bicarbonate of soda. Magnesium carbonate is less alkaline, but has the advantage of counteracting the constipating effect of calcium carbonate. Bismuth subcarbonate, in small doses, is soothing to the mucous membrane of the stomach. It is well to give 0.3 gm. of calcium carbonate and 0.3 gm. of bismuth subcarbonate, alternating every two hours with 0.3 gm. of sodium bicarbonate and 0.3 gm. of magnesium carbonate. Aluminum acetate has been advocated as both an astringent and a mild alkali. We have had no experience with it. Alakol, which contains an alkali in addition to aluminum acetate, has proved efficacious when given in doses of 0.5 gm. three times a day in a tumbler of water.

If there is the slightest evidence of alkalosis, that is, slight nausea, headache, twitching of the muscles, or if the Chvostek phenomenon is present, alkalies should be discontinued at once. After a patient has bled profusely, the hyperpnea that results from the loss of blood predisposes to alkalosis so that the addition of even a small amount of alkali may suffice to bring about a serious situation leading to fatal termination unless checked.

Silver Nitrate.—Many years ago Kaufmann advocated the use of silver nitrate 0.3 gm. to 250 cc. of water, 1 tablespoonful three times a day. Silver nitrate excites the secretion of mucus which tends to neutralize acidity. This treatment is an excellent substitute for alkalies. If given for a too long period, however, it may cause symptoms of argyria.

Gastric Lavage.—Sippy advocated washing out the stomach morning and night in order to keep acid secretions at the lowest possible level. We have not found this necessary.

If hypersecretion is markedly disturbing, jejunal feeding is the ideal remedy.

Olive Oil.—One-half to 1 tablespoonful of olive oil should be taken shortly before each meal. Later, it may be taken with lettuce, a little lemon being added.

Atropine or Novatropine.—Mention must be made of atropine sulfate (0.0006 gm.) or novatropine (0.005–0.03 gm.) by mouth, two or three times daily. It is quite true that atropine has no effect upon the quantity or quality of secretions. Nevertheless, it cannot be denied that the administration of this drug often has a most beneficial effect on hypersecretion. Its favorable influence we believe to be due to its paralyzing effect on the vagus, which is a motor, sensory and secretory nerve. If atropine serves only to reduce the irritability of the vagus, spasm is relieved and so is pain.

Prognosis

The vast majority of cases of gastric hemorrhage due to peptic ulcer will yield to medical treatment. In milder cases, treatment is effective within twenty-four to forty-eight hours. In the more severe cases, bleeding may show signs of ceasing within three or four days, but there may be tarry stools for as long as eight days. Occult blood may persist for fourteen, sometimes for as long as twenty-one days. After that, progress toward health is rapid. In about 5 per cent of cases the hemorrhage terminates fatally.

Prognosis is largely determined by the site of the bleeding. Unfortunately while it is in effect it is almost impossible to determine the site.

It is generally assumed that when there are tarry stools without hematemesis, the bleeding is from a duodenal ulcer, and that when hematemesis is the most marked symptom the bleeding is from a gastric ulcer. If tarry stools without hematemesis are accompanied by nausea and marked collapse, and if active treatment, including blood transfusions, has no marked effect within the first twenty-four to forty-eight hours, one should suspect that the bleeding is from a pancreaticoduodenal vessel and may terminate fatally. This is especially to be feared if, instead of tarry, the stools are dark

red in color, since this is an indication that the blood is passing from the duodenum into the rectum so rapidly that there is insufficient time for it to be converted into hematin. This can occur only if a large vessel has ruptured.

Indications for Surgery

Almost all clinicians agree that operation should not be undertaken *during* hemorrhage, with the rare exception of those cases in which the hemorrhage threatens to be fatal.

Regarding the advisability of surgery *after* the hemorrhage ceases, opinions differ. One's judgment should be guided by the frequency with which hemorrhage occurs. Some authors (including Lahey) estimate its recurrence at 20 per cent, but in our experience this figure is high. Surgical intervention is usually not indicated after one hemorrhage only, unless it be so exceptionally severe as to cause dread of its recurrence, or if the patient must be away on long journeys from a place where he would be safely within reach of adequate medical or surgical care in case of a recurrence.

If there is a second hemorrhage within a fairly short time (six months to a year), the patient should be operated upon as soon as feasible after the second hemorrhage. After a third hemorrhage, operation is obligatory.

After the acute bleeding has ceased and the patient has otherwise recovered he may have a lowered hemoglobin (70 per cent or less). If occult blood appears intermittently in sufficient quantities to account for the secondary anemia, it is best to advise surgical intervention. In the first place, protracted oozing awakens a suspicion of the development of cancer. Secondly, protracted oozing from an ulcer lowers local tissue resistance, hence healing of the ulcer becomes impossible and perforation may occur.

Regarding the kind of operation, if a patient has an ulcer that tends to bleed and a gastro-enterostomy is done, this may be followed by a jejunal or gastrojejunal ulcer with considerable risk of another hemorrhage. If he should have recurrence of the original ulcer or develop a new ulcer, hemorrhage is also likely to recur. Therefore, *subtotal gastrectomy* is the only satisfactory procedure.

BIBLIOGRAPHY

1. Winkelstein, Asher: Am. J. M. Sc., *185* (5): 695 (May) 1933.
2. Woldman, E. E. and Rowland, V. C.: Am. J. Dig. Dis., 2: 713, 1936; Am. J. Dig. Dis., *8:* 39, 1941.
3. Hurst, A.: Am. J. Dig. Dis., *8:* 321 (Sept.) 1941.
4. Ewald, C. A. and Ivy, A. C.: Virchow's Arch. Path., Anat. and Phys., p. 194, 1883.
5. Farrell, J. I. and Ivy, A. C.: Am. J. Phys., 76: 227, 1926.
6. Quiglay, P. J., Zettleman, H. J. and Ivy, A. C.: Am. J. Phys., *108:* 643, 1934.
7. Gray, J. S., Bradley, W. B. and Ivy, A. C.: Am. J. Phys., *118:* 463, 1937.
8. Hands, A. P., Fanley, G. B., Greengard, H., Preston, F. W. and Ivy, A. C.: Am. J. Phys., *133:* 314, 1941.
9. Friedman, M. H. F., Rechnagel, R. O., Sandweiss, D. J. and Patterson, T. L.: Proc. Soc. Exp. Biol. & Med., *41:* 509, 1939.
10. Sandweiss, D. J., Sugerman, M. H., Friedman, M. H. F., Saltzstein, H. C. and Farbmann, A. A.: Am. J. Dig. Dis., *8:* 371 (Oct.) 1941.
11. Friedman, M. H. F. and Sandweiss, D. J.: Am. J. Dig. Dis., *8:* 366 (Oct.) 1941.
12. Miller, Greer: Ann. Int. Med., *3:* 393, 1941.
13. Silverman, D. N. and Katz, R. A.: South. Med. J., *34:* 383 ff. (June) 1941.
14. Andresen, A. F. R.: J.A.M.A., *89:* 1397 (Oct. 22) 1927.
15. Meulengracht, E.: Acta Med. Scand. Supp., *59:* 375, 1934.
16. Chasnoff, J., Leibowitz, S. and Schwartz, R.: Am. J. Dig. Dis., 7: 9, 373–78 (Sept.) 1940.

THE SWEDISH HOSPITAL

THE CHOICE OF TREATMENT IN GASTRIC AND DUODENAL ULCERS*

J. WILLIAM HINTON, M.D., F.A.C.S.†

THOSE physicians interested in the care of patients suffering from gastric or duodenal ulcers, whether they be internists or surgeons, have come to a more general understanding of the limitations of both medical and surgical treatment during the past decade. This has been brought about by combined clinics for the treatment of both medical and surgical patients with ulcers, in which the personnel consists of both internists and surgeons. In such a clinic the good results from each method of treatment are soon appreciated and the bad results are evaluated so that one does not repeat the same errors.

It has been my privilege to spend fourteen years working in such a clinic. When the clinic was started in January, 1928, we believed, as a result of what we had seen in our surgical follow-up clinic, that operations generally gave poor results. For that reason we would not advise operative intervention in a patient with an ulcer unless the pain was so severe one was forced to operate by request of the patient. We immediately eliminated such "so-called" indications as pyloric obstruction, gastric ulcer, and severe massive hemorrhage without pain and advised medical care for all of these conditions. The above principles have not been deviated from during the entire fourteen years.

I felt from the beginning that medical care for the *uncomplicated* ulcer gave excellent results. I am more convinced of that now than in the early years of the clinic. From our

observations, if a patient with an ulcer is seen early in the course of the disease, meaning the first few months or year, and is put on medical management, and if he cooperates in the treatment, the chances of avoiding surgery over a ten-year period are excellent. Of course, if the patient with ulcer is first seen late in the course of the disease, five years or longer after the onset, then the chances of improvement from medical management are greatly diminished. In these instances the disease has generally progressed beyond the stage of a simple ulcer. Penetration of the entire wall of the stomach or duodenum has probably occurred and an associated pancreatitis exists which is causing the patient to seek medical aid. In these circumstances one cannot expect a cure by dietary management.

It is the failure to appreciate these very fundamental principles which has led to so much confusion about good and poor results from surgical procedures, particularly *gastro-enterostomy*. In the first few years of our clinic, 1928 to 1931 inclusive, gastro-enterostomy alone was practiced, but we were soon to see a large number of poor results which we could not at first explain. During this period of five years we referred twenty-nine cases for gastro-enterostomy, and in the fifth year an occasional case for subtotal resection. As all patients were transferred to the ulcer clinic after operation, we had there a large group of gastro-enterostomies under observation. The results from gastro-enterostomy were so generally unsatisfactory that it was discontinued in 1932 and since 1933 subtotal resections have been done exclusively. One will immediately challenge this stand but before forming judgment it would be well to examine all of the data we have.

A study of our cases in these early years of the clinic revealed that the percentage of operative cases was extremely small. We came to the realization that we were really performing operations only on patients with the complication of an ulcer, namely chronic pancreatitis, which could not be cured by short-circuiting procedures. In other words, if patients do not come to operation until the floor of the ulcer is formed by an adjacent viscus, which is usually the pancreas, then the failure of gastro-enterostomy is inevitable. On

the other hand, if gastro-enterostomy is performed before such a complication has occurred a good result may be expected provided the patient is fortunate enough to avoid a gastrojejunal ulcer. It is our belief, however, that the cases which are cured by gastro-enterostomy can be cured by a simpler method of treatment, namely, dietary management.

There is very little evidence that gastro-enterostomy restores the patient to health and an earning capacity quicker than does medical care. The findings in 106 gastro-enterostomies followed for an average of 7.1 years have been reported.[1] We found that only 24.5 per cent of the patients were cured. A letter follow-up or a recall of a group of patients for one thorough examination to determine the results of operation is misleading as to the true clinical picture over a period of years.

Having concluded in 1932 that gastro-enterostomy seldom cures a patient with a chronic ulcer, we felt justified in performing *subtotal resection* in all cases of chronic gastric and duodenal ulcers for which operation was indicated. Ninety patients have since been subjected to this procedure. The results are very satisfactory and so far gastrojejunal ulcer has not been observed in the cases which we have followed. Pernicious anemia has developed in one patient, who is being treated for that condition at the present time. We are now evaluating our results from subtotal resections and they will be reported in the near future.

It should be emphasized that in subtotal resection we always remove the ulcer whether it be duodenal or gastric. When the ulcer is left attached to the pancreas the results are not so good. In any evaluation of subtotal resection one should definitely distinguish between those cases in which the ulcer has been left attached and those in which it has been completely removed. The former operation is a compromise procedure and the latter a complete surgical procedure.

The question of medical or surgical management of *gastric ulcer* when it is first diagnosed is still being debated. We have discussed this problem previously,[2] and it will suffice to say here that gastric ulcers respond to medical care more readily

than do duodenal ulcers. If there is the least doubt as to the differential diagnosis between gastric ulcer and gastric carcinoma, an immediate operation is advised, but otherwise these cases are treated medically and an operation is advised only for uncontrollable pain. In about 10 per cent of gastric ulcers the differential diagnosis between an inflammatory lesion and a gastric cancer is difficult.

The *acute perforated ulcers*, whether they be gastric or duodenal, will require immediate surgical intervention after treating the shock by intravenous infusions of fluids or plasma. The surgical procedure consists only in simple closure of the perforation, after which the ulcer is treated as a medical problem, in the same manner as uncomplicated ulcer. If gastro-enterostomy is added to simple closure the incidence of gastrojejunal ulcer is higher than in instances of chronic duodenal ulcers treated by gastro-enterostomy. The procedure cannot be too strongly condemned.

Massive hemorrhage should be treated conservatively with transfusions, infusions, dietary management and sedation. The majority of patients will recover, but a small percentage of massive hemorrhages will prove fatal under medical care. The percentage will vary with different hospitals and also with the type of case. I am discussing cases in a municipal hospital with an active ambulance service and my remarks may not hold true for a hospital without an ambulance service. Our cases consist of those with secondary anemia with the red cell count below 3,000,000 and the hemoglobin below 60 per cent, and the patient is in shock. In a previous report,[3] based upon 165 cases in a twelve-year period, we found that 10 per cent proved fatal.

Since 1937 four patients with massive hemorrhage have been operated upon in the active stages of hemorrhage and all survived. In three instances subtotal resection was performed, as it was the only means of controlling the hemorrhage. Other procedures such as gastro-enterostomy and attempts to ligate the gastroduodenal artery would have been futile, since in two instances posterior duodenal ulcers were complicated by marked chronic pancreatitis and in one of these the bleeding was from the superior pancreaticoduo-

denal artery and in the other from a large branch of this artery. In another case a gastric ulcer on the lesser curvature had perforated the stomach wall and a large branch of the left gastric artery was bleeding. The final case was a gastro-jejunal ulcer which was perforating into the mesentery of the small gut and a large artery was bleeding from the mesentery. The gastro-enterostomy was dissociated.

Since 1937 we have not lost a case from massive hemor-rhage and we feel certain that the four cases described would have proved fatal if operation had not been done. There is a method of deciding the indications for surgical intervention in massive hemorrhage; this is the *transfusion test*. Trans-fusions in amounts of 1000 to 5000 cc. of blood are given by the indirect method and if the pulse and blood pressure have not improved or if they have become worse it is a fair indi-cation that we have arterial bleeding, which will prove fatal. The cases of massive hemorrhage needing operative interven-tion as a life-saving procedure are very few but they do oc-cur and one must be ready to meet the situation when the need arises.

BIBLIOGRAPHY

1. Church, Reynold E. and Hinton, J. William: The Results of Gastro-enterostomy in Gastric and Duodenal Ulcers. Surgery, 7: 647–656 (May) 1940.
2. Hinton, J. William and Trubek, Max: The Transformation of Gastric Ulcer into Gastric Carcinoma. Surg., Gynec. & Obst. 64: 16–21 (Jan.) 1937.
3. Hinton, J. William: Massive Hemorrhage in Peptic Ulcer; The Trans-fusion Test for Determining the Necessity of Operation. Ann. Surg., 110 (Sept.) 1939.

THE PREOPERATIVE AND POSTOPERATIVE PHYSIO-LOGIC BALANCE OF ULCER PATIENTS*

J. WILLIAM HINTON, M.D., F.A.C.S.†

and

McKINNIE L. PHELPS, M.D.‡

THE morbidity and mortality in gastric surgery are very closely related to the physiologic balance of the patient before, during and after the operation. During the past decade the surgeons doing gastric surgery have realized that their mortality has been more directly influenced by the proper physiologic balance of extracellular fluids, the correction of hypoproteinemia, and the choice and administration of the anesthetic agent than by any improvement in the technical steps of the operative procedure.

There are several objectives in preparing a patient with a chronic debilitating disease, such as peptic ulcer, for operation, and among these are (1) the ease of execution of the operative procedure without shocking the individual; (2) the prevention of chest complications; (3) the prevention of abdominal distention; and (4) the prevention of wound complications such as dehiscence and infections. If one pictures a patient with a chronic duodenal ulcer who has suffered for years from pain, is undernourished, anemic, and his economic status is such that he is seeking medical aid in a municipal hospital, then one can appreciate the type of case we are discussing in this presentation and the steps we have taken to restore these patients to normal before subjecting them to an operative procedure. The fluid balance receives first consideration, hypoproteinemia and vitamin "C" deficiency are treated, and the hemoglobin and red cell count are restored

to normal. An evaluation is made of the severity of the pain while the patient is in the surgical wards. If the pain has been relieved by bed rest he is not operated upon, but is referred for a further period of observation in the ulcer clinic, even though he may have been sent from the clinic for operation.

Between September 1, 1935 and March 1, 1941 we have referred for operation 75 ulcer patients upon whom the senior author has had occasion to operate. We wish to emphasize that these patients remained in the hospital seventeen days preoperatively and only nineteen days postoperatively. Although the majority of them had been under the observation of the senior author for months or even years, it was felt that still further hospital observation was essential to evaluate the pain correctly and make sure an operation was indicated. This took on the average of ten days. The following seven days were used in obtaining a state of complete physiologic balance to prevent the postoperative complications already mentioned.

The first consideration is the *preoperative restoration of a normal fluid and electrolytic balance.* As the ulcer patient who awaits operation is invariably dehydrated due to the continuous pain and occasional vomiting, the fluid administered was *normal salt solution*, which remains in the tissues longer than glucose preparations. It is well known that a normal person needs from 3000 to 3600 cc. of fluids daily to maintain a normal fluid balance. As 50 per cent of our body weight is in the intracellular fluids, and 20 per cent in the extracellular fluids, which is divided 5 per cent for the blood plasma and 15 per cent for the interstitial fluids, it is obvious that the latter is the first to be lost and will need replacement. This is accomplished by giving 2000 cc. of normal saline intravenously daily for seven days. Glucose with the saline solution is avoided because of its diuretic action. The question may be asked why salt solution is given by venoclysis when water could be administered orally. The former assures us that the patient is getting adequate fluid. A normal person in twenty-four hours takes 2000 to 2500 cc. of fluid as liquid, 500 cc. in the food and 500 cc. by oxidation. It is seldom that a patient with ulcer will take orally his normal fluid need of 3000 to

3600 cc. plus the quantity that is needed to correct the dehydration attendant upon the ulcer.

Tissue edema is not to be feared preoperatively, since the patient is ambulatory and the hypoproteinemia is corrected by transfusions which are used to correct anemia. *Postoperatively* the administration of fluids must be carefully watched lest they cause pulmonary edema with chest complications. With the extracellular fluid replaced before operation and the blood volume restored to normal, shock or peripheral circulatory collapse during or immediately following the operative procedure is prevented and the only demand for fluids is the normal daily requirement. Therefore, if the preoperative routine as given is followed, 1000 cc. of salt solution by venoclysis during the operation and 2000 cc. during the next twenty-four hours is the maximum amount required. The postoperative venoclysis should be limited to 1000 cc. at a time. Continuous postoperative venoclysis prevents frequent turning and provides in addition an excessive amount of fluid. It should be guarded against.

Secondary anemia should be completely corrected before operation, and with the blood banks and the indirect transfusions it does not offer the obstacles which formerly prevailed. There are two important reasons for correcting anemias. The first is, to restore the oxygen-carrying capacity of the blood, which is our way of preventing anoxia during and after the operation. Secondly, if the red cell count and hemoglobin are restored to normal we have overcome hypoproteinemia with its tendency to cause tissue edema and possibly wound dehiscence.

A *vitamin C preparation* in doses of 200 mg. is given intramuscularly for seven days preoperatively in all cases, on the assumption that the patient is deficient in vitamin C which may have a tendency to delay wound healing and cause wound dehiscence.

For twenty-four hours preceding operation *cathartics* are strictly avoided on the theory that, in any abdominal surgery excluding surgery of the small or large intestine, additional distention is produced by interfering with normal intestinal peristalsis. Therefore an *enema* is resorted to preoperatively.

Likewise all cathartics and enemas are avoided postoperatively and the patient usually has a normal bowel movement within three to four days. *Pitressin* is likewise avoided postoperatively for the same reason.

The stomach is never washed preoperatively unless a true obstruction exists, since a gastric hemorrhage occasionally results from such a procedure. A *Levin tube* is inserted one hour before operation and left open to permit drainage of the stomach throughout the operation. The tube is left unclamped and postoperatively the stomach is irrigated hourly with salt solution to remove all blood clots and mucus. As soon as the patient is conscious, water is given in any quantity desired by mouth. There will be no danger of distention if the tube is open and clean. The tube remains in for seventy-two hours, after which time the patient is on a selected soft diet.

The use of *morphine* preoperatively and postoperatively is an important consideration. In our series of seventy-five cases an average of 5 mm. of Magendie solution was given preoperatively and 15 mm. postoperatively. The excessive use of morphine postoperatively is a factor in chest complications. It is our policy to have these patients turn from side to side as soon as conscious and continue to do so once every hour while awake for the next forty-eight hours. This prevents the collection of secretion in the bronchi, with resulting atelectasis. If morphine is used in large doses the patient sleeps for long periods without moving, and the morphine abolishes the cough reflex which allows secretions to accumulate in the bronchi. Waters[1] refers to cough reflex as the "janitor of the respiratory tract" and warns against its being abolished by excessive medication.

The routine as described has been followed in a municipal hospital without special nursing care, and obviously the poor risks which we have encountered have been numerous. As stated previously, the average postoperative stay in our series of seventy-five cases was nineteen days. There were four deaths, one from pneumonia and three from peritonitis.

One essential in the management of the ulcer case is the *prevention of anoxia* during and after the operation. This has

been accomplished by proper hydration preoperatively so as to prevent shock or peripheral circulatory collapse, the correction of any existing anemia before operation, the use of morphine very sparingly so as to eliminate the cough reflex, and the hourly change of position which assists in deep respirations and prevents the accumulation of mucus in the bronchi.

The surgical principles of *gentle handling of tissue, complete hemostasis* and *careful wound closure* with nonabsorbable material have been a factor in preventing distention or abdominal complaints and thus have made the frequent turning of the patients much easier. Likewise the interest of the nursing staff and the resident staff in watching these patients carefully cannot be minimized as a very important factor in preventing chest complications in this series.

BIBLIOGRAPHY

1. Waters, Ralph M.: Anoxia: The Anesthetist's Point of View. J.A.M.A., *115* (Nov. 16), 1940.

are forerunners to such imbalances are still much of a mystery, and the pathogenesis of the condition is as varied as the clinical and experimental conditions concerned in its production.[2, 3, 4, 5,]

Recent advances in our knowledge of these substances have been reviewed by Ivy.[1] At least two of them may be somewhat directly concerned in the pathologic physiology of gastric or duodenal ulcers, namely *enterogastrone* and *urogastrone*, both of which exert an inhibitory action upon the motility and secretory response of the stomach. The former, obtained by extraction of intestinal mucosa, and the latter, derived from urine, are apparently identical in physiologic beneficial action upon the Mann-Williamson ulcers of experimental animals[1, 6, 7] and upon the gastric and duodenal lesions of human beings.[7] Sandweiss and his associates found that the secretion of free acid by the stomach was not necessarily inhibited by urogastrone. Furthermore, they believe "the beneficial effect is obtained in some manner through stimulation of fibroblastic and epithelial proliferation, and formation of newly formed blood vessels."

Our present knowledge of the autacoids produced within the gastro-intestinal tract hardly justifies extended discussion, as modes of preparation, the therapeutic action, methods of administration and side-effects are not as yet sufficiently well studied to be of practical value to the physician in the clinic or at the bedside.

Hormones Formed Outside the Gastro-intestinal Tract.— The ready availability and known potency and actions of a number of hormones secreted by endocrine glands outside the gastro-intestinal tract proper have afforded opportunity to analyze their influence and the influence of disturbances in the respective glands by which they are produced upon the development and course of peptic ulcers. Such effects cannot be considered entirely apart from the constitutional diathesis or from the neuronal pathways simultaneously involved.

THE CONSTITUTIONAL DIATHESIS

No type of body build is apparently immune to the development of gastric or duodenal ulcer, but several investi-

gators,[5, 8, 9] in the course of extended mensural studies, have
described a type of individual prone to the disease. Robinson[9]
made measurements in 250 male patients with ulcer and in
7478 controls of the same sex, as a result of which he finds
the ulcer patient different from the control in every respect
except height. He is normal or underweight, has a small thor-
acic and diminished abdominal circumference, with a rela-
tively smaller abdomen than chest. His blood pressure is low,
particularly the systolic reading. He is of slender, narrow,
linear build, possessing the so-called *asthenic habitus*. Among
the case records of 103 patients with ulcer, collected from
two general hospitals over a period of six years, and in which
the type of body build was stated, in only four did we find
the asthenic or lateral constitutional diathesis mentioned.

Whether the habitus above described can be directly re-
lated to glandular activity appears to be a moot question, but
the asthenic appearance and the low blood pressure suggest
a lowered adrenal function and an increased vagal activity.

NEUROHORMONAL RELATIONSHIPS

Nervous discharges and hormonal activity are coming into
closer and closer relationship with each other through the
efforts of a host of workers in neurologic, endocrinologic and
physiologic fields. The fact needs little emphasis here. The
fundamental anatomic structure and functional capacities of
the autonomic nervous system, the hormonal synergisms and
antagonisms of its two great divisions, and their influence
upon gastric and intestinal secretion and motility have re-
ceived a large share of attention. Through the maze of our
expanding knowledge of the hypothalamus, much of conjec-
ture has traveled with fact, but, broadly speaking, this area
of the brain appears to act in conjunction with the pituitary
in regulating many bodily functions, including water bal-
ance, carbohydrate, protein and fat metabolism, gastro-intes-
tinal motility and secretion, body temperature, total metab-
olism, and so forth. There seems to be little doubt that the
nervous system and endocrine glands work together to
control and regulate the majority of known bodily proc-
esses.[10, 11, 12]

The Anterior Pituitary

Disturbances associated with states of insufficiency predisposing to hypoglycemia will be discussed later. Our Case V (*q. v.*) illustrates some of the noteworthy points to be considered.

The Posterior Pituitary

Ulcerations in the gastric and intestinal mucosae have been produced[13, 14, 15, 16] and relieved[17] by the use of pituitrin and pitressin. However, the ulcerations produced in animals by the administration of relatively large amounts of posterior lobe extract do not resemble the lesions seen in cases of ulcer in human beings.

Rationalization of the use of pituitrin or pitressin in the treatment of gastric and duodenal ulcer is based upon several facts. Jores and Beck[10] observed nocturia in twenty-two of thirty-one patients with ulcer and in but two of twenty-four controls, and believed a lesion in the diencephalon played an active part not only in the disturbance of water balance but also in the manifestations of the gastric ulcer. Metz and Lackey[17, 18] noted similar disturbances of water balance with polyuria and nocturia in patients with a duodenal ulcer. A reduced secretory activity of the gastric mucosa has been noted following the use of extracts of the posterior pituitary in human beings.

These facts have led Metz and his associates[17] to administer posterior pituitary lobe powder to seventy-six patients with peptic ulcer. Forty milligrams of this material were given by insufflation four times daily, thirty minutes after each meal (for maximum effect in checking postprandial secretion) and at bedtime. Sixty-seven of these patients evidenced definite improvement not only in subjective symptoms but also in the appearance of the gastric mucosa after periods of treatment varying from three to six weeks. These investigators believe the slow absorption of the small doses used by insufflation increases gastric and duodenal blood flow by its antagonism to acetylcholine which in this location has the reverse effect. Larger doses would have a vasoconstricting action associ-

ated with a rise in blood pressure, a phenomenon which was absent in all but two of their patients.

In the following instance of the association of diabetes insipidus and both duodenal and intestinal ulcerations, all of the observed neurohormonal factors were confined to the posterior lobe of the pituitary and the supra-optic nuclei.

Case I. Diabetes Insipidus Associated with Duodenal and Intestinal Ulcerations

History.—A. C. was an unmarried thirty-year-old man with diabetes insipidus of twelve years' duration, and advanced pulmonary tuberculosis of at least one year's standing. For several years he had suffered from intermittent upper abdominal symptoms described chiefly as bloating, belching and mild epigastric pains appearing one-half to two and one-half hours after meals.

Examination.—Examination revealed a thin, stoop-shouldered, pale, cooperative, and well oriented individual; he weighed 49.5 kg. (108.9 pounds); his height was 169.2 cm. (66.6 inches); the lower measurements being 88.7 cm. (34.9 inches). Both the thoracic and abdominal circumferences were small. His blood pressure in mm. of mercury was 100 systolic, 70 diastolic, and pulse rate, 96 per minute. The apices of the lungs were sunken, and signs of a bilateral tuberculous process with cavity formation were evident. There were no abdominal masses or areas of tenderness.

His average daily urinary output was 14,000 cc. rising at times to as high as 24,000 cc. and being variously influenced by voluntary restriction and forcing of water and salt.

A glucose tolerance test (1.75 gm. glucose per kilogram of body weight) revealed the following blood levels expressed in mg. per 100 cc.: fasting 94.3; one-half hour, 141.8; one hour, 185.2; two hours, 200.0; three hours, 168.7. There was no glycosuria during the test. Urinary examinations were essentially negative except for specific gravities persistently below 1.004. The basal metabolic rate was —10. Tubercle bacilli were routinely present in the sputum.

Administration of Posterior Pituitary Extract.—Pituitrin, 2 cc. three times daily, was prescribed to control the diuresis. After one day, the patient refused such treatment because it so greatly increased his abdominal discomfort, and produced cramplike pain. During a period of two weeks, several changes in dose and dosage interval were made, but even 0.5 cc. of the solution four

The Anterior Pituitary

Disturbances associated with states of insufficiency predisposing to hypoglycemia will be discussed later. Our Case V (*q. v.*) illustrates some of the noteworthy points to be considered.

The Posterior Pituitary

Ulcerations in the gastric and intestinal mucosae have been produced[13, 14, 15, 16] and relieved[17] by the use of pituitrin and pitressin. However, the ulcerations produced in animals by the administration of relatively large amounts of posterior lobe extract do not resemble the lesions seen in cases of ulcer in human beings.

Rationalization of the use of pituitrin or pitressin in the treatment of gastric and duodenal ulcer is based upon several facts. Jores and Beck[10] observed nocturia in twenty-two of thirty-one patients with ulcer and in but two of twenty-four controls, and believed a lesion in the diencephalon played an active part not only in the disturbance of water balance but also in the manifestations of the gastric ulcer. Metz and Lackey[17, 18] noted similar disturbances of water balance with polyuria and nocturia in patients with a duodenal ulcer. A reduced secretory activity of the gastric mucosa has been noted following the use of extracts of the posterior pituitary in human beings.

These facts have led Metz and his associates[17] to administer posterior pituitary lobe powder to seventy-six patients with peptic ulcer. Forty milligrams of this material were given by insufflation four times daily, thirty minutes after each meal (for maximum effect in checking postprandial secretion) and at bedtime. Sixty-seven of these patients evidenced definite improvement not only in subjective symptoms but also in the appearance of the gastric mucosa after periods of treatment varying from three to six weeks. These investigators believe the slow absorption of the small doses used by insufflation increases gastric and duodenal blood flow by its antagonism to acetylcholine which in this location has the reverse effect. Larger doses would have a vasoconstricting action associ-

ated with a rise in blood pressure, a phenomenon which was absent in all but two of their patients.

In the following instance of the association of diabetes insipidus and both duodenal and intestinal ulcerations, all of the observed neurohormonal factors were confined to the posterior lobe of the pituitary and the supra-optic nuclei.

Case I. Diabetes Insipidus Associated with Duodenal and Intestinal Ulcerations

History.—A. C. was an unmarried thirty-year-old man with diabetes insipidus of twelve years' duration, and advanced pulmonary tuberculosis of at least one year's standing. For several years he had suffered from intermittent upper abdominal symptoms described chiefly as bloating, belching and mild epigastric pains appearing one-half to two and one-half hours after meals.

Examination.—Examination revealed a thin, stoop-shouldered, pale, cooperative, and well oriented individual; he weighed 49.5 kg. (108.9 pounds); his height was 169.2 cm. (66.6 inches); the lower measurements being 88.7 cm. (34.9 inches). Both the thoracic and abdominal circumferences were small. His blood pressure in mm. of mercury was 100 systolic, 70 diastolic, and pulse rate, 96 per minute. The apices of the lungs were sunken, and signs of a bilateral tuberculous process with cavity formation were evident. There were no abdominal masses or areas of tenderness.

His average daily urinary output was 14,000 cc. rising at times to as high as 24,000 cc. and being variously influenced by voluntary restriction and forcing of water and salt.

A glucose tolerance test (1.75 gm. glucose per kilogram of body weight) revealed the following blood levels expressed in mg. per 100 cc.: fasting 94.3; one-half hour, 141.8; one hour, 185.2; two hours. 200.0; three hours, 168.7. There was no glycosuria during the test. Urinary examinations were essentially negative except for specific gravities persistently below 1.004. The basal metabolic rate was —10. Tubercle bacilli were routinely present in the sputum.

Administration of Posterior Pituitary Extract.—Pituitrin, 2 cc. three times daily, was prescribed to control the diuresis. After one day, the patient refused such treatment because it so greatly increased his abdominal discomfort, and produced cramplike pain. During a period of two weeks, several changes in dose and dosage interval were made, but even 0.5 cc. of the solution four

times daily still produced colic for short periods of time following its administration. The patient was changed to the intranasal application four times daily of 40 mg. of posterior pituitary powder. This relieved not only the polyuria, which was reduced to 2400 cc. in twenty-four hours, but also caused the disappearance of the abdominal symptoms, except on days when there were rather gross dietary indiscretions.

Postmortem Observations.—The patient died of his tuberculosis approximately two months after the described treatment was instituted. As a result of a postmortem examination, the following diagnoses were made: bilateral caseous ulcerative tuberculosis of the lungs, to which death was attributed; amyloidosis of the liver, spleen and kidneys; ulceration of the small intestine, etiology not determined; degeneration of the supra-optic nucleus and of the posterior lobe of the pituitary gland in association with diabetes insipidus.

Of special interest in the necropsy findings were the condition of the small intestine and the hypothalamus. The mucosa of the duodenum was congested; the first portion showed two small ulcers, the larger with a crater 0.3 cm. in diameter; both were in a state of healing. The terminal ileum showed several transverse ulcers with ragged and necrotic bases and irregular edges, with but slight evidence of fibroblastic repair. On microscopic examination, a tuberculous origin could not be proved for any of these lesions.

The entire hypothalamic area with attached pituitary was studied grossly and by serial section. The only abnormal findings were a complete bilateral atrophy of the supra-optic nuclei and tracts, and a replacement fibrosis of the posterior pituitary.

Comment.—The aggravation of intestinal symptoms by large, rapidly absorbed doses of pituitrin and the relief from smaller doses by insufflation suggest that the conception of Metz and his associates concerning the influence of posterior lobe extracts may be a correct one. The origin of the ulcerations is not clear. That none of them were tuberculous seems to be well proven by histologic studies. It seems likely that the nutritional state of the patient, his body build, and the generalized toxemia resulting from his active tuberculous process produced or at least contributed to the production of the ulcer state. On the other hand, the disturbances in water balance and the unopposed constrictive action of acetyl-

choline in the splanchnic area may have been responsible. It is noteworthy that no tendency to hypoglycemia was observed in the post-absorptive state or in connection with the appearance of abdominal distress.

THE SEX HORMONES

The equal sex incidence of ulcer in the prepubertal years as contrasted with the inequality in adult life speaks for the strong influence exerted by the gonads upon this condition.

The preponderance of peptic ulcer in the male has for a long time raised the question of the protective influence of female sex hormones. Little attention has been paid to the direct causative role which male sex hormones may assume.

A number of facts point toward the conclusion that anterior pituitary-like hormone, estrogens and, possibly, progesterone exert a favorable action upon peptic ulcers, while anterior pituitary extracts containing the gonadotropic factor aggravate the ulcer condition. Sandweiss and his associates[19] found but one proved case of peptic ulcer among 70,310 consecutive hospital admissions of pregnant women. Other abdominal lesions occurred with usual frequency. In twenty-five women with ulcer who became pregnant, twenty in thirty-seven pregnancies were completely symptom-free, while four in fourteen pregnancies had nausea, gas and vomiting during the first two to three months and were then symptom-free. Only one had ulcer symptoms throughout pregnancy, and she delivered prematurely. Thirty women with ulcer were studied for endocrine abnormalities. Seven showed hypopituitarism or hypogonadism, or both; three had a mild hyperthyroidism; two, a hypothyroidism; and two others, nontoxic adenomata of the thyroid gland. Eighteen, or 60 per cent, had passed through the *menopause* or presented unequivocal signs and symptoms of that state.

Winkelstein[20] confirms the high incidence of ulcer at the menopause. Forty of ninety female patients developed their first symptoms at that time. All showed relief of ulcer and menopausal symptoms upon the administration of adequate amounts of ovarian follicular hormone, with a return of symptoms at varying intervals following the withdrawal of

therapy. He suggests that the ovarian follicular hormone suppresses the function of the anterior pituitary hormone, which in excess is known to influence ulcers adversely.

Experimentally, Sandweiss and his associates[19] demonstrated the fact that the life of Mann-Williamson dogs could be prolonged by the use of anterior pituitary-like hormone, and that at death 50 per cent showed no ulcers while an additional 20 per cent presented ulcers in various states of healing. Two to 5 cc. injections of this hormone daily had no effect on the free and total acid secretion either in the human or in the dog. A high percentage of patients injected with like amounts noted subjective improvement, but the authors believed this was no greater than the relief obtained by other products parenterally administered.

Case II. Menopausal Ulcer Syndrome

History.—S. E., a forty-seven-year-old woman, was admitted to the hospital because of weakness, loss of weight, palpitation, tachycardia, nervousness, dizziness, abdominal pain and insomnia. These symptoms had begun several months after a supravaginal hysterectomy three years previously, at which time, however, neither tubes nor ovaries were disturbed. Her abdominal discomfort was more of an epigastric distress than actual pain, appearing in from one to two hours after meals, often subsiding spontaneously, but promptly relieved by food or alkali.

Examination.—The patient was a well developed and nourished individual with no evidence of organic disease on physical examination.

On admission, the urinalysis was negative, and the blood count was completely normal. A six-hour glucose tolerance test yielded the following values for blood sugar in mg. per 100 cc.: 129.0, 217.4, 162.6, 153.8, 111.1, 113.0, and 117.0; the concomitantly passed urine specimens were sugar-free. Other blood chemical analyses in mg. per 100 cc. were: fasting blood sugar, 90.7; urea nitrogen, 11.1; sodium, 385.0; and potassium, 12.7. The basal metabolic rate was +1; the tracing showed numerous long, sighing respirations.

The patient's electrocardiographic tracing showed changes characteristic of the menopause.[21, 22] Roentgenograms of the gastro-intestinal tract revealed an ulcer in the first portion of the duodenum.

Estrogenic Hormone Therapy.—Under treatment with estrogenic hormone (progynon dipropionate, 1 mg. weekly) and a smooth diet, not only the patient's menopausal but also her ulcer symptoms promptly disappeared. The patient did not diet carefully after a period of six weeks. Despite this fact, six months after beginning treatment and two months after hormone therapy had been stopped, roentgenograms of the duodenum failed to reveal either a pylorospasm or an ulcer niche.

Comment.—This patient had had no children throughout the period of active sexual life, although no contraceptives had been used. She showed no obvious stigmata of endocrine disturbances. On the contrary, she was well proportioned, although distinctly of the linear, asthenic or ptotic type of body build. Subjective symptoms and objective findings of the climacterium as well as the ulcer syndrome were relieved by adequate estrogenic hormone therapy.

GLANDS CONCERNED IN CARBOHYDRATE METABOLISM

The evidence for a disturbed carbohydrate metabolism in peptic ulcer has been thoroughly presented by Ask-Upmark,[4] who leans strongly to the conception that liver dysfunction, hypoglycemia and diencephalic disturbances act in a somewhat vicious circle upon the secretory and motor activity of the stomach by way of the vagus nerve. The focal point of his discussion is the *hypoglycemia* observed in the course of oral glucose tolerance tests. Typical curves show a normal or subnormal fasting level of blood sugar, an early high rise often suggesting a diabetic or prediabetic state, and a late fall to hypoglycemic levels. These changes are attributed by Ask-Upmark primarily to liver damage as demonstrated by galactose-tolerance tests, with the pituitary, the adrenal and the hypothalamic centers acting in a secondary role. It seems logical to assume that all these factors may be involved, but it is an attractive hypothesis to believe that at least in some cases the glandular or diencephalic involvement precedes that taking place in the liver. Both Sandler[23] and Ask-Upmark,[4] as well as other observers quoted by them, note that the ulcer pain appears during the hypoglycemic phase. Sandler has

successfully relieved the distress by the use of low carbo-
hydrate diets which avoid the rapid changes in blood sugar
producing increased motor activity of the stomach via dien-
cephalic-vagal pathways.

Case III. Ulcer Syndrome Apparently Related to Hypoglycemia

History.—M. T., a forty-three-year old male, developed a
peptic ulcer two and a half years ago following excessive mental
and physical strain. Pertinent facts in the past history included
abnormal hunger since early childhood, worse when tired, and
often only relieved by rest. For a number of years prior to the
discovery of the ulcer he had suffered from faintness and an
"all-gone" feeling in the pit of the stomach several hours after
meals, these symptoms being sometimes associated with sweating,
especially after the evening meal and when unusually tired.

The patient's abdominal distress was usually relieved by alkali,
but was always better from taking food. The type of food taken
was important. Pain recurred most promptly and with greatest
severity after a purely carbohydrate feeding, particularly of
concentrated sweets. Single blood specimens taken at the times
when the patient complained most bitterly of the pain, the "all-
goneness," the weakness and the sweating invariably yielded
values for glucose below 0.65 per cent, and on one occasion, as
low as 0.45 per cent.

Nocturnal pain was one of the outstanding features of this
patient's condition. Such pain occurred between 2 and 4 A.M.,
and was never completely relieved by alkali, but always promptly
removed by food. Blood sugar taken during one such episode was
51 mg. per 100 cc.

Examination.—The patient was a well developed and nourished
male, with a height of 162.5 cm. (64 inches), and a weight of 71.3
kg. (156.8 pounds). He was of the sthenic or lateral type of body
build with full face, short, thick neck, and relatively broad
shoulders. The blood pressure in mm. of mercury was 108 sys-
tolic and 75 diastolic.

The presence of duodenal ulcer was confirmed by roentgenog-
raphy. The results of a six-hour glucose tolerance test, expressed
in milligrams per 100 cc., were: 80.3, 120.4, 135.4, 126.2, 75.1,
58.0, and 82.1.

Treatment.—Symptoms have been relieved by frequent feed-
ings of a diet containing approximately 90 gm. carbohydrate, 90
gm. of protein, and 100 gm. of fat. This has been calculated on

a basal maintenance requirement of 1800 calories so divided that carbohydrate furnishes approximately 20 per cent, protein 20 per cent, and fat 60 per cent of the calories, respectively.

Comment.—Here there seems to be no question about the relation of pain to low blood sugar levels. The distress was often not relieved by alkali alone, but invariably relieved by food; it was worse after sweets or a high carbohydrate meal, and minimal when a high fat, low carbohydrate diet was taken. Of course the possible influence of enterogastrone cannot be ignored in this connection.

Ask-Upmark[4] adduces interesting clinical facts to substantiate the important role of hypoglycemia in the pathogenesis of the ulcer syndrome, to wit:

1. Peptic ulcer and diabetes mellitus are rarely seen together.

2. In persons with normal storage of glycogen in the liver, ulcer is infrequent.

3. Ulcer is almost unknown in patients with underfunction of the eosinophilic elements of the pituitary.

4. Ulcer is commonly noted as a late manifestation of untreated Addison's disease.

5. Ulcers are common in burns, where hypoglycemia is a frequent finding.

The presence of ulcer in inadequately treated Addison's disease has been observed by us in but one instance:

Case IV. Peptic Ulcer in Inadequately Treated Addison's Disease

History.—L. H., a fifty-three-year-old woman, was admitted to the hospital complaining of pigmentation of the skin, weakness, anorexia, loss of weight, upper abdominal pain, nausea, vomiting, and an occasional attack of diarrhea. Because of weakness, she had been confined continuously to bed for the six weeks prior to admission, and when first seen, showed in addition to her earlier symptoms marked disorientation. Her pigmentation had begun two and one-half years previously, and the other symptoms had been of gradual onset and increasing severity since that time.

Examination.—The outstanding physical findings included marked emaciation, generalized darkening of the skin to almost

black about the extensor surfaces over joints. There was pigmentation of the buccal mucous membrane. The heart was small, the blood pressure in mm. of mercury. 55 systolic, 40 diastolic. When the patient's condition permitted their determination, the weight was 33.9 kg. (74.6 pounds), and the height. 161.0 cm. (63.4 inches). Laboratory examinations confirmed the diagnosis of Addison's disease with crisis.

Course.—The patient's upper abdominal pain was interpreted as a part of the syndrome so commonly seen in crisis. until it persisted well into the third week of hospitalization, and showed a tendency to be relieved by food, for which, as soon as crisis was controlled. the patient evidenced more than an average desire. Gastro-intestinal roentgenograms revealed a pylorospasm. with poor filling of the duodenal cap, and an ulcer niche in the postpyloric area. This improved under appropriate therapy; the presence of ulcer could not be confirmed on an examination made six months later. Determinations of the blood sugar levels were made at or about the same time as each of the x-ray studies, both before and after the administration of glucose. Each series of determinations revealed a high tolerance for sugar, with no appreciable difference in the configuration of the curves on the two occasions.

Comment.—The improvement noted in this patient was probably the result of the generally improved nutritional state, rather than a specific influence of treatment upon carbohydrate metabolism. This is borne out by the fact that the clinical symptoms subsided while the patient was receiving desoxycorticosterone acetate, which is known to have no direct influence upon intermediary carbohydrate metabolism, and particularly no effect upon the storage of glycogen in either the liver or the muscles.

Case V. Concomitant Influence of the Hypothalamus, the Pancreas and, Probably, the Adrenals and Ovaries upon the Course of Peptic Ulcer

History.—Z. W., a twenty-nine-year-old colored woman, had complained for five days of continuous epigastric pain radiating to the back below the scapulae on both sides. More or less constant nausea, blood-tinged vomitus aggravated by eating, and occasional tarry stools accompanied and aggravated the pain.

The patient stated that she was perfectly well until three years previously, since which time she had had gradually increasing "hunger" pains, appearing in the epigastrium shortly before meals. This pain had always been relieved by food, but only incompletely by alkalies.

During the past year the patient had lost 36 pounds, developed amenorrhea, and noted an increase in the severity of all her other symptoms. A diagnosis of multiple ulcers of the duodenum with duodenal obstruction was made and confirmed by x-ray six months prior to the present admission. Her catamenia was established at the age of fifteen and, until the present amenorrhea began, recurred regularly at thirty-day intervals and lasted four days with moderate flow.

Examination.—Physical examination revealed a markedly emaciated, asthenic individual in whom the only positive findings were a blood pressure in mm. of mercury of 95 systolic and 60 diastolic, and some tenderness in the epigastrium.

On admission to the hospital, fasting values for the chemical constituents of the blood in milligrams per 100 cc. were: urea nitrogen, 45; nonprotein nitrogen, 70; creatinine, 2.7; glucose, 35 (later, 50 and 33, respectively); ceritamic acid, 0.71; chlorides, 442; sodium, 335; potassium, 15.1; total cholesterol, 150; esters, 102. Plasma proteins in milligrams per 100 cc. were: fibrinogen 0.61; albumin, 3.53, and globulin, 2.20. The blood Wassermann was negative. The sedimentation rate was 3 mm. in fifteen minutes; 45 mm. in one hour (Westergren method). Occult blood was found in the feces on more than one occasion. The bromosulfalein test revealed no retention at the end of thirty minutes. The results of galactose tolerance and Takata-Ara tests were negative. The carbon dioxide combining power of blood serum was 65 volumes per cent.

Blood sugar values in milligrams per 100 cc., fasting and at half-hour intervals after the oral administration of 100 gm. of glucose, were: 35, 84, 84, 100, 100 and 80. In order to eliminate the factor of poor absorption, 50 gm. of glucose were given intravenously, and blood sugar determinations were made at fifteen-minute intervals with results as follows, in milligrams per 100 cc.: 45, 312, 340. 165, 150, 70 and 35.

Fractional gastric analysis with specimens taken at fifteen-minute intervals yielded total acid values of 65, 85, 50, 53, 55, and 53. respectively. and a free hydrochloric acid titer of 50, 48, 48, 42, 48, and 44, respectively. Occult blood was present and lactic acid bacilli were absent. Roentgenograms of the gastro-

intestinal tract revealed a perforating ulcer of the duodenum with partial gastric obstruction.

Operation.—The stomach was resected 10 cm. above the pyloric opening. At the time of laparotomy, a perforated duodenal ulcer and a large inflammatory mass involving the pylorus and the pancreas were found. The head of the pancreas was firm and indurated, and made free from the duodenum with difficulty. The pathological specimen confirmed these findings and showed the presence of an acute pancreatic edema. The islands of Langerhans appeared normal.

Subsequent Course.—Six days postoperatively a fasting blood glucose was 30 milligrams per 100 cc.; two weeks later, 60; and four weeks later, 120. An oral glucose tolerance curve three weeks after operative procedure showed values in milligrams per 100 cc. of blood at half hourly intervals of 80, 90, 110, 105, and 95, respectively. The serum lipase and amylase on repeated examination were within normal limits. On two occasions postoperatively, estimations of blood proteins revealed a slightly lowered total figure and a reversal of the albumin-globulin ratio. Hemoglobin reached a low of 22 per cent with a simultaneous decrease in the red blood cells to 1,000,000. Urinalyses, blood nonprotein nitrogen constituents, chlorides and carbon dioxide combining power were normal throughout the postoperative course.

Postmortem Observations.—Important necropsy findings included the presence of 2 liters of a light yellow, cloudy fluid in the peritoneal cavity in which many fibrous flakes floated. There was, however, no generalized peritonitis. Between the left lobe of the liver, the diaphragm, and the lower end of the sternum, the left diaphragmatic dome, the transverse colon, a portion of the stomach, and the upper portion of the anterior abdominal wall, there was a pouch 20 to 30 cm. in diameter filled with a thick, yellowish-brown material. There was a large abscess just below the pancreas, reaching to the upper pole of the left kidney, from which about 100 cc. of pus was evacuated.

The undersurface of the liver, the distal portion of the stomach, the pancreas, the duodenum and the transverse colon were matted together by dense fibrous tissue. The gallbladder showed many fibrous adhesions. The liver and gallbladder together weighed 1440 gm. On section the liver appeared reddish-brown in color and somewhat flabby with a normal arrangement of lobules. The pancreas weighed 80 gm., was adherent to all neighboring organs, and yet on section showed only moderate congestion. There were extensive superficial ulcerations in the mucosa of

the jejunum just below the anastomosis. Both adrenals showed several small adenomata. The ovaries were small, but otherwise normal in appearance.

Significant microscopic findings were an albuminous degeneration and cloudy swelling of the liver; multiple terminal emboli of both kidneys, with old glomerulonephritis; nodular hyperplasia of the cortex of both adrenal glands; an interstitial pancreatitis with foci of multinuclear giant cells and areas of abscess formation; and active but immature graafian follicles in both ovaries, but no corpora lutea.

Anatomical Diagnoses.—Status after gastric resection with gastrojejunostomy for peptic ulcer; pulmonary embolus; subdiaphragmatic abscess; intra-abdominal abscess; septicemia; ascites; bilateral hydrothorax; hydropericardium; adenoma of adrenals; bilateral diaphragmatic pleurisy; cause of death, septicemia.

Comment.—Evidence for pancreatic and hypothalamic involvement was present in this patient. From the history, one gains the impression that an increased vagal tone with hyperinsulinism and increased secretory and motor activity of the stomach appeared before any of the other changes. As the condition progressed, the vicious circle of Ask-Upmark[4]—hypoglycemia, vagotonia, diencephalic damage, decreased liver function, further lowering of blood sugar level and so forth—was established. The high postoperative blood sugar levels are not easily explained unless it be on the basis of an increased adrenal response to a septic state.

There was no evidence of disturbance of the posterior lobe of the pituitary in this patient; moreover, the lesions produced in the gastro-intestinal tract by the administration of extracts of this lobe, in no way resemble those of gastric or duodenal ulcer commonly seen in the human being.

Extracts of the anterior lobe of the pituitary containing the gonadotropic factor, and extracts of pregnancy urine (A.P.L. factor) have been shown to have a beneficial effect on the healing of ulcers of the duodenum and jejunum.[24] Moreover, where they are present in excess, peptic ulcer does not develop.[21] Some features in the present case are indicative of severe underfunction of the anterior lobe of the pituitary, bordering on the clinical picture of Simmond's cachexia. The emaciation, the weakness, the amenorrhea, the low basal

metabolic rate, the decreased blood sugar and so forth, especially point in this direction. With the exception of the amenorrhea, all of these findings can be readily explained in other ways. It hardly seems likely, however, that the patient's nutritional state as a result of pyloric obstruction was sufficiently severe one year before coming under observation to produce a complete cessation of menstruation.

It seems evident that the development of peptic ulcer represents a complex chain of events in which not only the stomach, but also the duodenum, the glands which pour their secretion into it, and neurohormonal disturbances in the pituitary, the hypothalamus and the adrenal all play a part.

SUMMARY

1. Some of the factors concerned in the pathogenesis of peptic ulcers have been illustrated by reference to five cases.

2. The constitutional background, neurohormonal interrelations, and glandular associations of peptic ulcer have been discussed.

3. The probable influence of the anterior and posterior pituitary, the gonads, the pancreas and the adrenals on the development and course of gastric and duodenal ulcerations has been mentioned.

BIBLIOGRAPHY

1. Ivy, A. C.: Some Recent Advances in the Physiology of the Alimentary Tract. Am. J. Digest. Dis., *8*: 361–365 (Oct.) 1941.
2. Sanders, L. C.: The Etiology of Peptic Ulcer. Rev Gastroenterol., *8* 30–35 (Jan.–Feb) 1941.
3. Held, I. W.: Pathogenesis of Peptic Ulcer. Rev. Gastroenterol., *8* 350–357 (Sept.–Oct.) 1941.
4. Ask-Upmark, E.: Further Observations on the Pathogenesis of Peptic Ulcer. Acta med. Scandinav., *103:* 380 ff. (March 8) 1940
5. Rabinovitch, J., Pines, B and Teicher, I. Pathogenesis and Pathologic Changes in Peptic Ulcer, and Production of Pain Arch Int. Med., *67:* 620–636 (March) 1941.
6. Friedman, M. H. F. and Sandweiss, D. J. The Gastric Secretory Depressant in Urine. Am. J. Digest. Dis., *8*. 366–371 (Oct.) 1941.
7. Sandweiss, D. J. and associates The Effect of Urine Extracts on Peptic Ulcer, an Experimental and Clinical Study. Am J Digest Dis., *8* 371–373 (Oct.) 1941.
8. Draper, G. The Human Constitution. W. B Saunders Co., Philadelphia, 1924.

9. Robinson, S. C. and Brucer, M.: The Body Build of the Male Ulcer Patient. Am. J. Digest. Dis., 7: 365–373 (Sept.) 1940.

10. Jores, A. and Beck, H.: Nykturie und Ulcurkrankheit. Klin. Wchnschr., 14: 526–530 (April 13, June 15) 1935. Abstr. in: J.A.M.A., 104: 2220 (June 15) 1935.

11. Kennedy, Foster: The Hypothalamus: Pacemaker of Metabolic and Emotional Rhythm. J.A.M.A., 114: 2092–2095 (May 25) 1940.

12. Grinker, Roy R.: Hypothalamic Functions in Psychosomatic Interrelations. Psychosom. Med., 1: 19–47 (Jan.) 1939.

13. Dodds, E. C., Hills, G. M., Noble, R. L. and Williams, P. C.: The Posterior Lobe of the Pituitary Gland: Its Relationship to the Stomach and to the Blood Picture. Lancet, 1: 1099–1100 (May 11) 1935.

14. Dodds, E. C. and Noble, R. L.: The Relation of the Hypothalamus to the Pituitary Gland. Brit. M. J., 2: 878–880 (Oct. 31) 1936.

15. Franchini, G.: Die Funktion der Hypophyse und die Wirkungen der Injektion ihres Extraktes bei Tieren. Berlin klin. Wchnschr., 47: 613, 670, 719, 1910.

16. Metz, M. H.: A Gastric Lesion Produced by Posterior Pituitary Extract. Texas State J. Med., 34: 295–297 (Aug.) 1938.

17. Metz, M. H. and Lackey, R. W.: Peptic Ulcer Treated by Posterior Pituitary Preparations. Am. J. Digest. Dis., 7: 27–32 (Jan.) 1940.

18. Metz, M. H. and Lackey, R. W.: The Treatment of Peptic Ulcer with Posterior Pituitary Extract. Texas State J. Med., 52: 589–590 (Jan.) 1937.

19. Sandweiss, D. J., Saltzstein, H. C. and Farbman, A. A.: The Relation of Sex Hormones to Peptic Ulcer. Am. J. Digest. Dis., 6: 6–12 (March) 1939.

20. Winkelstein, A.: A Possible Relationship between the Ductless Glands Secreting the Sex Hormones and Peptic Ulcer. J. Mt. Sinai Hosp., 7: 29–31 (May–June) 1940.

21. Scherf, D.: The Respiratory and the Circulatory System in Females with Ovarian Dysfunction. Ann. Int. Med., 13: 1414–1430 (Feb.) 1940.

22. Scherf, D. and McGavack, T. H.: The Estrogen-like Action of Desoxycorticosterone Acetate upon the Altered Electrocardiogram Seen in Various Hypo-ovarian States. Am. J. M. Sc. In press.

23. Sandler, B. P.: The Pain Mechanism in Peptic Ulcer and Pseudo-ulcer Syndrome. The Control of These Disorders with a Low Carbohydrate Diet. Rev. Gastroenterol., 7: 485–500 (Nov.–Dec.) 1940.

24. Kalk, H. and Meyer, P. F.: Blutzuckerspiegel und Magensekretion. Ztschr. f. klin. Med., 120: 692–714, 1932.

GASTROSCOPY IN THE DIAGNOSIS OF DISEASES OF THE STOMACH*

GORDON McNEER, M.D., F.A.C.S.†

GASTROSCOPIC examinations have been carried out successfully for a time sufficiently long to enable us to arrive at a critical opinion regarding their clinical usefulness. An individual limiting his practice to such work is very apt to exaggerate the actual importance of the method. The average roentgenologist is so satisfied with the results obtained by fluoroscopic and radiographic methods that he has no time to delegate to the study of gastroscopy. The surgeon says that he is going to explore the patient in any event and so he does not intend to subject his patient to gastroscopy. He asks the gastroscopist if he has discovered any early resectable gastric cancers not diagnosed by other methods. The latter is forced to say that it has occurred on only one or two occasions during the course of over two thousand such examinations. What then can be the value of direct visualization of the stomach?

The material upon which this discussion is based has been studied in five large metropolitan hospitals. The purpose of the investigator has been to establish the correct diagnosis in each case, not to weigh the advantages of any one diagnostic procedure. In most instances the same person has likewise either operated upon the surgical material or attended such operations, hence a more truly critical point of view has been developed. *The only conclusion possible is that gastroscopy is of great importance in the study of diseases of the stomach when employed by a trained observer.*

Inflammatory Diseases

Gastritis is a term, shelved in the past but recently brought to light, that still confuses the conscientious physician. Instead of clarifying the subject, gastroscopy has frequently added to the confusion.

The standard classification of the gastritides is as follows: (1) acute; (2) superficial hypertrophic; (3) chronic hypertrophic; and (4) chronic atrophic.

Chronic atrophic gastritis is such a distinct endoscopic entity that more definite statements about it can be made. This process may be localized or generalized and is easily recognized by even the neophyte. The involved area takes on a dirty grayish color through which course many tiny blood vessels, patterned after the branching twigs of a tree. This arborization is a distinct feature of atrophic gastritis and is always present in this disease. Such a condition is frequently but not always found in patients suffering from vitamin deficiency diseases, pernicious anemia, gastric neoplasms and from unexplained causes.

Although it is the end stage of chronic gastritis, atrophy is by no means an absolutely irreversible state, as has been shown by Benedict, Abels and McNeer, and others. Whereas achlorhydria invariably accompanies diffuse chronic gastric atrophy, the latter is by no means constantly associated with achlorhydria. Normal gastric mucosa, even hypertrophic rugae, are frequently seen in stomachs which are incapable of secreting hydrochloric acid after the injection of histamine.

Chronic atrophic gastritis cannot be visualized by fluoroscopic or radiographic methods and has been demonstrated time and again by endoscopy. It produces such symptoms as belching, heartburn, diarrhea and fullness after meals which can be relieved by the appropriate medication.

Chronic hypertrophic gastritis, on the other hand, is a difficult diagnosis to establish. Various states of gastric insufflation can produce a fullness or flattening of the rugae which must confuse even the most experienced observer. That a definite entity called "chronic hypertrophic gastritis" does exist is not denied by the author. This process produces

an inflamed thickening and enlargement of the rugal pattern which shows little change during insufflation. Instead of the bright orange-red color typical of the normal mucosa, the light reflex is definitely diminished and dull. When such a picture is visualized a definite opinion can be rendered that chronic hypertrophic gastritis is present. Such a state may exist in the antrum extending into the pyloric canal, even producing partial pyloric obstruction. Radiographically such

Fig. 127.—Roentgenogram in chronic hypertrophic gastritis.

problems have been confused with antral carcinoma. Gastroscopic investigation has usually clarified the diagnosis and obviated exploratory laparotomy.

No consistent correlation exists between chronic hypertrophic gastritis as shown radiographically and endoscopically (Figs. 127, 128). The large linear filling defects seen on the greater curvature of the fundus on many x-ray films and interpreted as gastritis are almost never seen endoscopically as hypertrophied rugae. The word "hyperrugosity"

probably better explains the redundancy of mucosal folds so often seen in the gastric fundus. The superficial variety is not distinct enough to warrant discussion.

Acute gastritis may be erosive, hypertrophic, or phlegmonous. The acute variety occurs in the stomachs of chronic alcoholics and is satisfactorily treated by withdrawal of the exciting cause. The mucosa takes on a bright inflamed appearance, often dotted here and there with superficial ero-

Fig. 128.—Gastroscopic view of stomach shown in Fig. 127 chronic hypertrophic gastritis

sions which look exactly like small canker sores. This process likewise appears in the mucosa of the stomach subjected to gastrojejunostomy, most especially in the presence of hyperacidity. It is most pronounced adjacent to the stoma although it may appear as a more diffuse process. Frequently the disease is so extensive that the mere gentle passage of the gastroscope over the inflamed mucosa will produce minor bleeding. Otherwise unexplained gastro-intestinal bleeding has been solved by endoscopy in the case of such patients. The symp-

toms are those of acute ulcer. Gastroscopy differentiates very often between recurrent or so-called "marginal ulcer" and acute gastritis of the postoperative stomach.

Postoperative Stomach

Surgical intervention so changes the normal contour of the stomach as studied by radiographic methods that frequently a definite diagnosis cannot be established by any means other than gastroscopy. Visualization of huge, turgid, edematous and inflamed rugae is ample explanation of ulcer-simulating symptoms. The demonstration of a peristomal or marginal ulcer can likewise be effected if one is present.

The stomach subjected to *partial gastrectomy* is especially suited to endoscopic examination. Here again direct visualization is superior to the relief study of radiographic methods because of the distortion produced by the operative treatment. This is particularly true when studying a *postoperative* stomach resected for carcinoma. The presence or absence of recurrence may be ascertained with fair certainty. A state of chronic atrophic gastritis frequently supervenes in these patients. That severe hemorrhage can occur from this parchment-like membrane has been demonstrated in at least one instance in our experience. Prior to her gastroscopic examination this patient was suspected of having a recurrence of her gastric sarcoma. The passage of five years since the date of suspected recurrence is sufficient support of the endoscopic as opposed to the fluoroscopic opinion in this particular instance.

Prepyloric Lesions

Pyloric stenosis offers difficulties to the radiologist which should be surmounted by the competent gastroscopist. Differentiation between prepyloric and postpyloric ulcer or even a small pyloric cancer causing obstruction to the gastric outlet offers difficulties to the radiologist which frequently are insurmountable. The well trained gastroscopic observer can readily determine whether or not there is a prepyloric lesion present. If none can be demonstrated the obstructing process can be assumed to be duodenal and therefore due to a benign

duodenal ulcer. In the presence of demonstrably active peristalsis through the entire pyloric segment, one can be reasonably certain that no infiltrating or ulcerative lesion exists in this area. Such a differentiation is of real importance in the case of older subjects as it is well known that simple gastro-enterostomy is the operation of choice if the pyloric obstruction is due to chronic duodenal ulcer. Partial gastrectomy with its added risk should be urged though reserved for all prepyloric lesions causing obstruction.
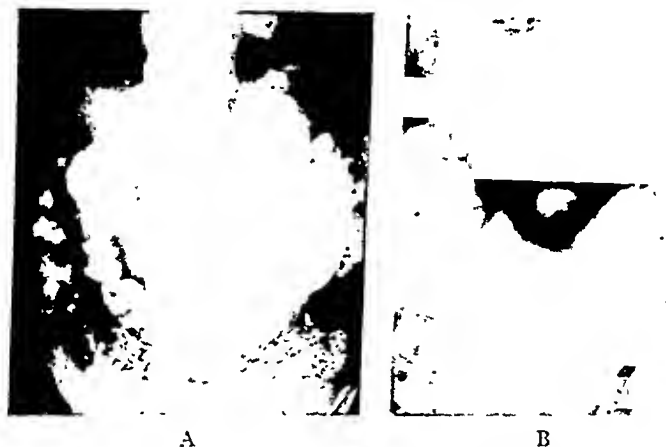
Fig. 129.—*A*, Roentgenogram of stomach demonstrating huge antral "filling defect" described as carcinoma. *B*, Same stomach after three weeks' therapy on an ulcer regimen. Gastroscopy demonstrated a normal stomach. The "filling defect" was spasm secondary to duodenal ulcer.

Differentiation of Benign and Malignant Gastric Ulcer

It is the opinion of this observer that accurate differential diagnosis between benign and malignant gastric ulcer cannot be consistently established by endoscopic or any other means except microscopic study of excised specimens. On two recent occasions, ulcers which have shown all signs of healing, when confirmed by visual examination of the resected gastric specimens by one of the real experts in pathology, have presented incontroversial evidence of underlying cancer by histopathological study. The experience of seeing many gas-
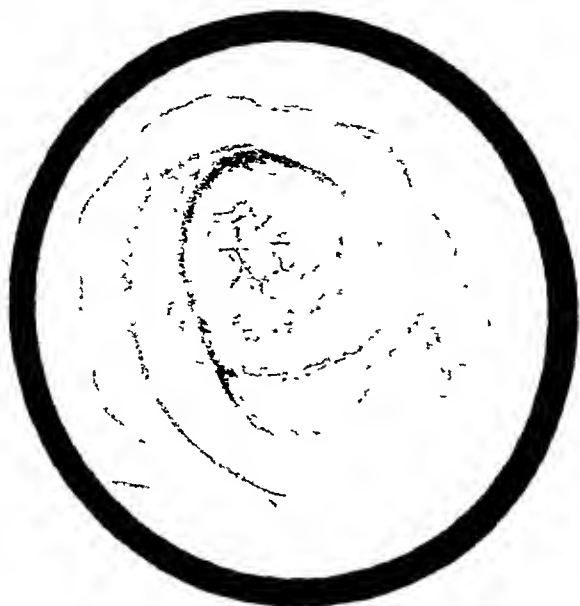
Fig. 130.—Normal antrum and pyloric canal demonstrated gastroscopically in same stomach shown in Fig. 129.

Fig. 131.—Gastroscopic demonstration of small operable cancer of pyloric antrum.

tric ulcers heal gastroscopically is a gratifying one, thus confirming the radiographic and clinical impression of a cure. Such patients should be examined at frequent intervals for one year before their release from careful observation. The endoscopic criteria for both ulcer and carcinoma are just as

Fig. 132.—Gastroscopic demonstration of benign gastric ulcer at incisura

definite and conclusive as are all others—and just as often completely upset by microscopic examination of the operative specimen.

Comment

The average office patient does not object to gastroscopic examination as much as to other endoscopic procedures. Owing to the preliminary cocainization of the oropharynx, this method of study causes less distress than gastric lavage or intubation for gastric analysis. Because the interior of the stomach has actually been visualized the subject feels particularly reassured when told by the examining physician that no disease exists in the organ under suspicion.

The *training of competent observers* is the most important aspect of the problem now that a satisfactory instrument is available. Too many physicians employ diagnostic instruments of all kinds without being willing to spend an adequate

period of training before extending their use to private patients. This practice is particularly to be condemned in the case of gastroscopy. Instead of discovering the presence of a gastric lesion passed over by the radiologist, a diseased stomach will be declared innocent, until such a time when both the unsuspecting patient and physician will be all too aware of its real nature.

There should be no rivalry between gastroscopy and radiography. Each method has its fundamental place in the establishment of correct diagnosis of gastric lesions. It is the summation of all our knowledge which offers the patient the greatest possible benefit of our experience, and to the accurate diagnosis of diseases of the stomach, gastroscopy will no doubt continue to make a real contribution.

GASTRITIS

ARTHUR L. HOLLAND, M.D.*

Acute and chronic gastritis may be, and usually is, the result of some kind of trauma to the gastric apparatus, whether it comes through intemperance, overindulgence, inadequate mastication, irritating materials like tobacco and alcohol, or through hematogenic bacterial infection or toxic matters locally operative; gastritis may be a part of the reflex indigestion of gallbladder disease and chronic disease of the lower right abdominal quadrant, the circulatory stases of cardiovascular renal disease or reflexes through chronic fibrosis of the lungs. It may come about through anatomic irregularities as in vagotonia or in the deficiencies or excesses of the endocrine system. It can and frequently is induced by emotional stress alone. All of these possibilities are well known and appreciated by most internists.

The indigestion that comes as a reflex and is made evident only through spasm may here be excluded, but there probably is never a prolonged spasm of any part of the gastric muscularis that does not cause irritation of the mucosa. This may be a very superficial form of gastritis, a mere "flush" as seen by the gastroscopist, but it is a definite change. Or it may represent profound changes in all coats of the gastric walls.

I will not dwell on these phases of gastritis. It is the ultimate possibilities of gastritis that I would stress; gastric ulcer, carcinoma and pernicious anemia, for example. We have for years known that gastritis may be a concomitant of ulcer and carcinoma. Thanks to the gastroscope, we are beginning to know that in gastritis we may and undoubtedly do have a

* Consulting Physician, Mount Vernon and Horton Memorial (Middletown) Hospitals and New York Infirmary for Women and Children; Consulting Gastro-enterologist, New York Hospital.

factor—perhaps an important one—in the etiology of these lesions.

In my own experience, and in that of others, as recorded in the literature, there have been many cases in which gastritis has preceded, by many years, the onset of cancer. Doctors Carey, Macnider and Ylvisaker[9] state that in Jenner's analysis[10] and in their own experience with gastritis, pernicious anemia and cancer, gastritis *conditions* the individual for either cancer or pernicious anemia, or both. Jenner's diagram[10] is as follows:

> Not: Pernicious *anemia* → Cancer
> But: Chronic gastritis → Cancer
> ↓ Mucosal atrophy
> Pernicious anemia

CLASSIFICATION

I briefly mention the classification (Lockwood's) that was employed many years before the development of the x-ray technic for rugal pattern study, and long before the invention of Schindler's gastroscope. This classification for limited clinical purposes is still usable, particularly in the acute forms.

Acute Catarrhal Gastritis.—(*a*) dietetic or simple gastritis; (*b*) infectious gastritis or food poisoning; *Membranous Gastritis*—secondary to diphtheria, typhoid, typhus, pyemia, etc.; *Phlegmonous Gastritis* (acute interstitial gastritis)—cause always microbic with alcohol often a predisposing factor; *Toxic Gastritis*—due to chemical irritants such as concentrated alkalies and acids, metallic salts, arsenic (fruit sprays), mercury, silver, etc.

Lockwood[1] classifies chronic gastritis thus: (*a*) those cases with hyperacidity; (*b*) those cases with normal acidity; (*c*) those cases with anacidity or achylia. This is obviously an incomplete classification. It does not describe the type of inflammatory change, its extent, or its location.

Schindler's[2] classification of gastritis "is based on a co-relation of gastroscopic findings with the course and progress of the disease. (1) Superficial gastritis; (2) atrophic gastritis; (3) hypertrophic gastritis; (4) gastritis of the postoperative stomach."

GASTROSCOPY

With only a bystander's limited experience in gastroscopy, I quote from McNeer and Barowsky[3]:

"In *superficial gastritis*, the stomach has the appearance of a definite inflammatory reaction taking place. The color is dusky red, and the mucous membrane is dull in appearance. There are hyperemic areas and erosions of varying size and hemorrhagic spots may also be seen. Occasionally gray patches of tenacious adherent mucus are observed.

"In *hypertrophic gastritis*, the outstanding impression that the observer gets is the marked increase in size of the rugae. In some cases, there does not appear to be any marked inflammatory reaction. However, the mucous membrane may appear thickened and swollen. The nodular formations which have been described frequently in the literature, we have only observed rarely. In some cases there is also a definite inflammatory reaction, here, it becomes more difficult to distinguish it from superficial gastritis.

"In *atrophic gastritis*, the mucous membrane appears thin and pinkish gray in color. The rugae are either effaced or markedly thinned out and in some cases a fine network of veins is observed.

"We have also observed a type of gastritis which is limited in extent. It may be confined to the antrum of the stomach. This antral gastritis may be any of the three varieties mentioned. Another type of gastritis that is frequently seen is in *gastro-enterostomized stomachs*. Here the inflammation is usually peristomal in extent and may be severe in inflammatory reaction. This reaction in the stomach has been observed in patients even several years after their operation."

The Significance of Exaggerated Mucosal Folds

I dare say that many a gastric mucous membrane has been thrown into accordion plaits as the result of *emotional stress*, or even fear in anticipation of a gastroscopic or x-ray investigation. The frequent absence of rugal hypertrophy in gastritis cases at autopsies, even when formalin has been introduced into the stomachs of the recently deceased subjects, suggests that the vegetative nerves of the deceased have ceased to operate rather than that obscuring postmortem changes have taken place.

Ruffin and Brown[4] have demonstrated by the gastroscope that the deep folds usually accepted by roentgenologists as

characteristic of gastritis can often be obliterated through *air inflation.* They suggest that the usual air inflation necessary in gastroscopy may flatten out normal rugal folds and thus throw doubt on at least some gastroscopic diagnoses of atrophic gastritis.

Gastritis is not always localized in the gastric mucous membrane. It may involve all parts of the gastric wall. *Interstitial gastritis* is characterized by such changes.

The vegetative nervous mechanism is often involved and the rugae may thus be shown as exaggerated folds which become inflamed because of an irritated muscular layer beneath.

Allergy could explain such phenomena through its effect on the muscle behavior by way of the vegetative nerves. We should not ascribe to exaggerated folds unwarranted significance—at least, the exaggeration is not always an expression of inflammatory changes in the mucous membrane itself. Increase in size and number of the secretory cells of the gastric membrane, because of long *overstimulation,* may be responsible for the redundancy of the rugal folds, but this probably comes more often through a pulling up of the irritable spastic muscle fibers beneath.

Foot[12] states that actual thickening of the folds is to be demonstrated in some specimens, due to inflammatory changes, and to increase in size and number of the secretory cells, particularly the mucous cells.

CLINICAL AND X-RAY DIAGNOSIS

As an occasional roentgenologist, I have not spent too much time in speculating on the general subject of gastritis, its etiology and pathology. I have, however, been particularly interested in antral gastritis, and that form of productive gastritis involving the greater curvature of the gastric fundus—not that I might add to my knowledge of the etiology and pathology of these lesions, but because they have given me so much trouble in differential diagnosis.

The use of the *gastroscope* in this field is invaluable, but it has limitations. It is in those cases in which it is not possible to employ the gastroscope, because of the patient's fears, or perhaps owing to his physical condition, that we must still

rely upon the clinical signs, the stomach tube and the x-ray.

In the interpretation of the *x-ray films* taken of these parts it has been found of value to use a "fingerprint" method in differentiating exaggerated rugal markings from infiltration of carcinoma. We all see these disquieting films from time to time. I have watched several such cases over a period of years, expecting at each check-up to have disclosed to me some evidence of neoplastic involvement.

In some of these cases much time and worry could have been saved had we carefully examined the different films for changes in the rugal arrangements. This pattern can and does change from time to time in gastritis, but in carcinoma it remains fixed or progresses in an orderly manner.

To be of real value these films should always be taken under the same conditions—a small water and barium meal of the same quantity and consistence in all of the examinations. The prone position and balloon pressure give the best results. When such films are taken at intervals over a period of time and are studied separately and superimposed one upon the other, one can usually differentiate cancer from a productive gastritis. The prints of the films in case II, to be presented later, will illustrate these points.

SYMPTOMS

The symptoms of *chronic gastritis* are not clear-cut. Nausea is usual, particularly in the atrophic form in which there is a degree of vagotonia present. Early satiety is here the rule. An epigastric pressure distress and occasionally epigastric soreness after meals may be experienced, and also vomiting after large meals of unsuitable foods. In rare cases, streaks of blood will be found in the vomitus. Mucus in the vomitus or in the extracted test meal is characteristic. This is intimately mixed with the food returns. It is thick and tenacious and does not float on the top of the specimen as does swallowed nasopharyngeal mucus. Most of these signs and symptoms are met with in any form of indigestion, whether it be that of cancer or of any of the gastro-intestinal neuroses.

Alcoholic gastritis gives the most constant signs and symptoms. Here we have early morning retching and vomiting, usually with mucus, occasionally with blood streaks, and a chronic laryngitis may persist and the pharynx is always irritable. These symptoms coupled with the alcoholic facies can hardly be misinterpreted.

Since the clinical evidence of chronic gastritis is so vague and irregular, and often completely lacking, we must rely upon gastroscopic examinations and x-ray studies better to understand this disease and differentiate it from more serious organic diseases such as ulcer and cancer.

ILLUSTRATIVE CASES

Case I. Acute Gastritis Resulting from Arsenic Poisoning, and Merging into Chronic Form

Miss C. S., a children's nurse-governess, aged forty-two years, was referred to me on December 9, 1941. Her illness had begun one and a half years earlier, with epigastric soreness and vomiting. Much gas pressure was experienced at irregular times and always after eating. She complained of a dry throat most of the time.

The patient was at that time admitted to the hospital under Dr. Warren Titus, where he made a thorough study of the problem. The general physical examination, x-ray studies and Wassermann test were reported as negative. The total gastric acidity was 114 and the free hydrochloric acid was 110. The hemoglobin concentration was 13.2 gm. per 100 cc. of blood, the red blood count 4,570,000, the white blood count 6800 and the differential count normal.

The patient was in the hospital for about three weeks, and discharged much improved. She had been given a bland diet, vitamin medication, and sodium thiosulfate. After discharge from the hospital she remained symptom-free for almost a year, except for a "weak stomach." She then had a recurrence of the nausea, vomiting and epigastric distress.

Again three weeks before the present check-up, December 9, 1941, she reported poor appetite and dryness in the throat. She had vomited recent food and some mucus several times immediately after eating. She felt rather weak during this attack, but this weakness was only temporary.

Our radiographic studies at the time were negative, except for the exaggerated rugal pattern throughout the stomach, par-

Fig. 133.
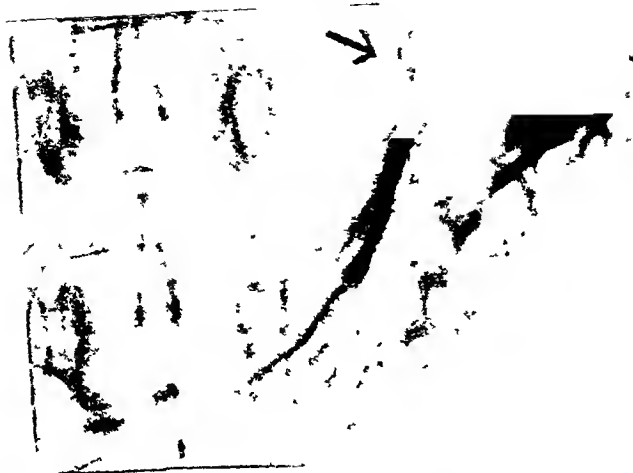
Fig. 134.

Fig. 133 (Case I, December 9, 1941).—The hypertrophied rugal folds are shown. The pattern is reasonably regular, and there is no evidence here of cancer. The arrow points to a rugal fold caught transversely.

Fig. 134 (Case I, December 14, 1941).—A distortion of the greater curvature of the stomach is apparent. This could be mistaken for a classical cancer defect.

ticularly in the pars media of the greater curvature. The small intestine studies were negative for any form of ileitis (Figs. 133, 134).

Gastric analysis gave a return of 20 cc., normal type mucus $+$ $+$; total acid 58; free hydrochloric acid 40; occult blood negative. The urine was normal throughout, except for a faint trace of albumin.

Arsenic had been found in the urine in her first hospital experience, and several months later it was again found.

This case illustrates a fairly common form of acute gastritis merging into a chronic form. The cause is often difficult to recognize. It is usually due to indiscriminate spraying of fruit trees.

Shortly before the onset of the trouble the fruit trees all about the grounds, including a vine growing up beneath the patient's window, had been heavily sprayed with an *arsenic* solution. The patient noticed unpleasant sensations on breathing when her window was open. She had eaten of the sprayed fruit. The practice of Europeans of dipping their grapes and other fruits in their table water is a practical preventive measure and not an affectation.

The high cost of the arsenic test is probably responsible for our not recognizing this form of poisoning more readily. It is interesting that the small intestine did not show any effects of the poisoning as it so often does.

The patient has reported, December 18, 1941, almost complete relief, but she finds that she can take only small meals in frequent feedings of reasonably bland foods. It is unfortunate that we were not permitted to use the gastroscope in this case. This patient will no doubt ultimately recover but will likely continue to be sensitive. Condiments and alcohol will never be a comfort to her.

In the x-ray films (Figs. 133, 134) note the coarse and deep rugae, particularly on the greater curvature of the fundus. We have in some such cases mistaken similar or more exaggerated distortions for neoplastic infiltration. This is always a difficult problem, but it can usually be settled through gastroscopic studies.

Case II. Antral Gastritis Probably Secondary to Duodenal Ulcer

M. S., a professional man, aged fifty years, was admitted January 18, 1926. Indefinite gastro-intestinal symptoms, such as

slight nausea and intense salivation at irregular times without relation to meals, had been present for six years prior to admission. The attacks would last about a week, with relief following for a month or more. There was no pain at first, except for a slight ache in the lower right quadrant. This was thought to have been due to a stone in the right ureter, which later on was passed followed by relief of the pain, but the nausea continued.

Prior to this, while in France in the army, the patient suffered severe diarrhea, which lasted for over a month, and since then on rare occasions has had looseness of the bowels.

On January 2, 1926, following a large family dinner with somewhat more alcohol than usual, the patient began to experience gnawing epigastric pains with nausea and lack of appetite. The pain was only slightly relieved by food and alkalies, but otherwise it had no relation to the time of eating. It continued for six days. Vomiting ensued and persisted for a short time after that. There was a small quantity of blood in the vomitus—on one occasion a small clot. The salivation first complained of persisted. Before the onset of this pain he had been given a solution of iodine presumably for the salivation, but this had only caused nausea and vomiting and was soon discontinued.

Findings of the physical examination at this time were negative, except that there was a definite but not marked tenderness in the epigastrium and slightly to the right. The general physical examination was essentially negative throughout.

Gastric analysis gave a return of 10 cc.; total acid 50; free hydrochloric acid 40; occult blood positive +; thick mucus + +.

Radiographic examination showed the chest organs to be apparently normal, also the esophagus, stomach (Fig. 135, *A*) and all three parts of the duodenum except that there was considerable antral spasm. The colon, twenty-four hours later, was found radiographically to be quite normal throughout. The appendix was not visualized. It was probably retrocecally placed. There was no tenderness in this region. A diagnosis of subacute antral gastritis was given, and the patient was placed on a bland diet. He responded at once to this treatment, and was fairly well for about three months.

At that time, April 7, 1926, a defect of the lesser curvature of the duodenal bulb was seen and the antrum had assumed a peculiar outline (Fig. 135, *B*). It looked as though there was a penetrating defect on its greater curvature. Gastric analysis this time showed total acid to be 76; free hydrochloric acid 46; occult blood negative; thick mucus + +.
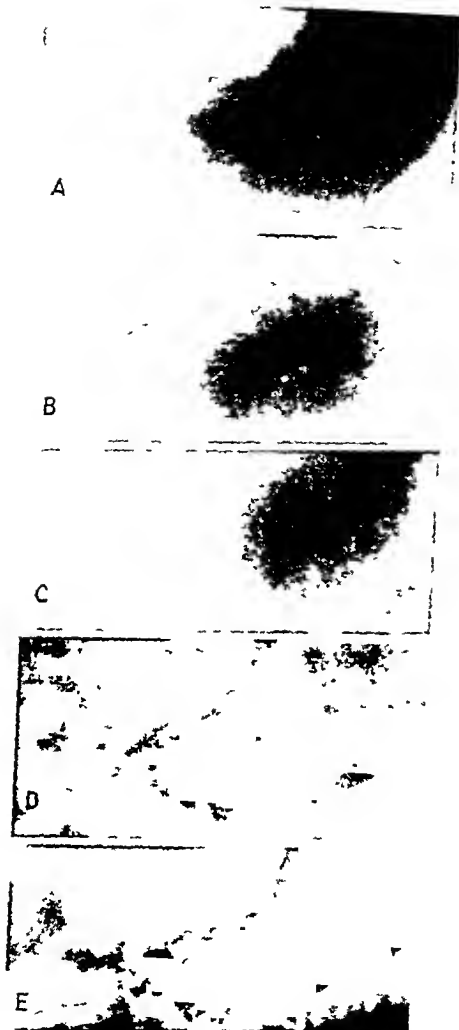
Fig. 135 (Case II).—*A*, Jan. 18, 1926. This film shows the duodenal bulb to be normal, except for a small incisura on the greater curvature. Under fluoroscopic manipulation this was filled out normally. The distortion of the gastric antrum is apparent. It suggested neoplastic involvement.

B, April 7, 1926. A different pattern of the exaggerated rugae is apparent. The duodenal bulb is seen to be defective under fluoroscopic manipulation.

C, Mar. 10, 1930. This suggests "fingerprinting" of the antrum; bulb defective.

D, Nov. 20, 1931. This film shows the rugal pattern to have changed

E, Sept. 26, 1941. Again the rugal pattern of the antrum has changed.

The patient was then given a neutralizing powder of magnesium, soda and bismuth. This appeared to relieve him considerably and he remained reasonably well for a year while following the bland diet and taking the neutralizing powder.

Our next radiographic examination, March, 1930, showed the duodenal defect clearly, and the antrum was very irregular in outline, but pliable (Fig. 135, C). These films suggested the possibility of neoplastic degeneration, but the pliability of the part under fluoroscopic manipulation, and the high acid, made this possibility seem remote. Permission for an exploratory operation was refused. The appendix was visualized and appeared to be normal.

In November, 1931, the same defects were visible, but the antral defect could be effaced through hand pressure, and the rugal pattern had changed (Fig. 135, D). Gastric analysis gave a return of 15 cc.; total acid 96; free hydrochloric acid 86.

In 1940 the patient reported having had no symptoms since the last examination except a sense of nausea at irregular times and occasionally the salivation previously complained of. Since that time until the present, many films have been taken and they always show the defective duodenal bulb and the irregular rugal pattern of the antrum with marked defects in its contour (Fig. 135, E). It is apparent, however, in comparing these films that the antral defects are never quite the same, and under fluoroscopic manipulation they can always be pressed out. The acid values have remained high and usually there has been mucus in the gastric returns, particularly when nausea has been a feature.

It is in this form of gastritis that we would expect help through the gastroscope, but we have not been permitted to use it. One interesting feature in this case is the occurrence of *duodenal ulcer*. We did not in the first few examinations recognize the defect of the bulb, and the symptoms were never too suggestive of this disease. It has been suggested by some who have examined the patient and the films, that the antral defects could have been caused by adhesions secondary to the duodenal lesion. I cannot agree with this because of the pliability of the antrum, and because the rugal pattern changes in every set of films that have been taken over a period of sixteen years. That the gastritis is secondary to the peptic ulcer is reasonable to believe. Alcohol may have been

a contributing factor. While the patient for years regularly took alcohol, it was never to such an extent that in itself it could have been responsible, but it may have been a predisposing cause.

The *appendix* as a reflex cause has·been considered. Chronic disease in the lower right quadrant often does cause intense antral spasm operating through the ileopyloric reflex. It is likely that antral gastritis can thus be brought about, but in this case we are apparently dealing with a normal appendix.

TREATMENT

There is no specific treatment for gastritis. It is largely *dietetic* and *expectant*, which really means that we do not
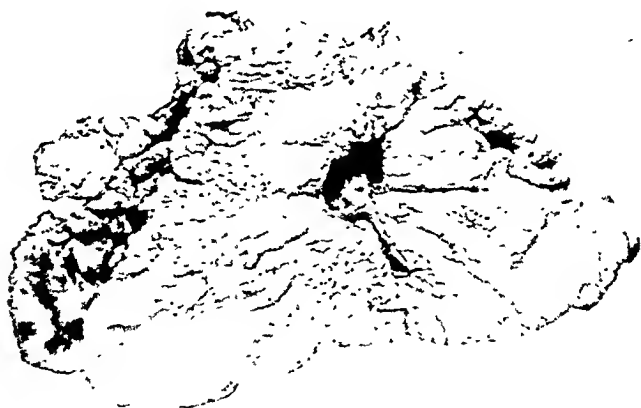
Fig. 136.—Carcinoma of the stomach with surrounding generalized atrophic gastritis. (From the Pathological Museum of the Cornell University Medical College, New York.)

know what to do outside of using the classical acid mixture, when the acid is low or absent, or by giving an alkaline powder with bismuth in hyperchlorhydria. If there are pain and soreness, orthoform (2 or 3 grains orally) or anesthesin may prove to be temporarily helpful. Mild, well diluted saline laxatives may be tried. Olive oil before meals is often a comfort. Lavage is contraindicated since it removes the

valuable protective mucus and only traumatizes a sensitive membrane.

A bland frequent-feeding diet is essential along with well regulated general hygiene. If vitamin medication is indicated,

Fig. 137.—Perforated ulcer of the stomach with hypertrophic ulcer gastritis. (From the Pathological Museum of the Cornell University Medical College, New York.)

care must be used to avoid stomach irritation. In alcoholic gastritis, large parenteral doses of thiamine hydrochloride should prove of some value.

BIBLIOGRAPHY

1. Lockwood, George R.: Diseases of the Stomach. Lea & Febiger, Philadelphia, 1913.
2. Schindler, Rudolf: Gastroscopy. University of Chicago Press, 1937.
3. McNeer, Gordon and Barowsky, Harry: A Gastroscopic Study of the Incidence of Chronic Gastritis in Common Gastric Afflictions. Am. J. Digest. Dis., 6: 180–183 (May) 1939.
4. Ruffin, Julian M. and Brown, Ivan W., Jr.: The Occurrence of Gastritis as Diagnosed by Gastroscopy in Gastric Neuroses. Am. J. Digest. Dis., 7: 414, 418 (Oct.) 1940.
5. Crohn, B. B.: Chronic Gastritis: Clinical Aspects. Bull. New York Acad. Med., Series 2, 15: 392–405 (June) 1939.

6. Schindler, R. and Murphy, H. M.: Symptomatology of Chronic Atrophic Gastritis. Am. J. Digest. Dis., 7: 7–14 (Jan.) 1940.

7. Schindler, R.: The Clinical Significance of Gastroscopy. Rev. Gastroenterol., 6: 122–127 (March, April) 1939.

8. Robertson, H. E.: Ulcerative Gastritis and Residual Lesions. J.A.M.A., 22: (Jan. 7) 1939.

9. Carey, James B., Macnider, Wetherby and Ylvisaker, R. S.: Gastric Observations in Achlorhydria. Am. J. Digest. Dis., 8: 401 (Nov.) 1941.

10. Jenner, A. W. F.: Perniziöse Anämie und Magenkarzinom. Acta Med. Scand., 102: 529, 1939.

11. Swalm, W. A. and Morrison, L. M.: Gastroscopic and Histologic Studies of the Stomach with Gastric and Extra-Gastric Disease during Life and at Autopsy. Am. J. Digest. Dis., 8: 391 (Oct.) 1941.

12. Foot, N. Chandler, Surgical Pathologist, New York Hospital: Personal communication.

COMMON DIGESTIVE DISORDERS OF INFANTS AND CHILDREN

PHILIP COHEN, M.D.*

VOMITING

In the Newborn:

VOMITING in a newborn baby is most frequently of a *functional* nature. Some babies swallow a great deal of amniotic fluid in the process of being born and vomit in order to rid the stomach of this foreign irritating matter. Every newborn baby suffers more or less from shock, and if feeding is begun before this has worn off vomiting is apt to ensue. Too rapid nursing is another cause of vomiting. The *hypertonic child*, with an excessive irritability and tonicity of his voluntary and involuntary systems, vomits with great facility. This may occur to such an extent as to suggest pylorospasm, but, aside from failure to gain weight, the symptoms are not alarming and quickly improve. Phenobarbital in doses of ⅛ grain three or four times daily is sometimes quite effective in controlling the vomiting and restlessness in cases of exaggerated vomiting. Other forms of functional vomiting, such as due to overeating and gulping of food, readily respond to reduced milk and caloric intake.

More violent forms of vomiting which arouse greater alarm in the newborn baby occur in *milk allergy*, which responds immediately to the omission of cow's milk and the substitution of another type of feeding, namely, goat's milk, or a formula derived from soy bean, or amino acids, mixtures which are now available commercially.

Much more serious is the early vomiting of *congenital intestinal obstruction*. Vomiting beginning from birth and continuing with a rapid down-hill course in a newborn baby

---

* Attending Pediatrist, Beth Israel and Bronx Hospitals.

6. Schindler, R. and Murphy, H. M.: Symptomatology of Chronic Atrophic Gastritis. Am. J. Digest. Dis., 7: 7–14 (Jan.) 1940.
7. Schindler, R.: The Clinical Significance of Gastroscopy. Rev. Gastroenterol., 6: 122–127 (March, April) 1939.
8. Robertson, H. E.: Ulcerative Gastritis and Residual Lesions. J.A.M.A., 22: (Jan. 7) 1939.
9. Carey, James B., Macnider, Wetherby and Ylvisaker, R. S.: Gastric Observations in Achlorhydria. Am. J. Digest. Dis., 8: 401 (Nov.) 1941.
10. Jenner, A. W. F.: Perniziöse Anämie und Magenkarzinom. Acta Med. Scand., 102: 529, 1939.
11. Swalm, W. A. and Morrison, L. M.: Gastroscopic and Histologic Studies of the Stomach with Gastric and Extra-Gastric Disease during Life and at Autopsy. Am. J. Digest. Dis., 8: 391 (Oct.) 1941.
12. Foot, N. Chandler, Surgical Pathologist, New York Hospital: Personal communication.

genital nature, particularly malrotation of the intestines with volvulus, is not infrequently met in older infants. Roentgen studies will reveal this disorder which is usually amenable to good surgical technic.

In Children:

In children, the most common single cause of vomiting is a *psychogenic and neurogenic imbalance*. It is amazing to see at how early an age vomiting can be a mechanism of defense or rebellion. This may become habitual and continue with slight cause for years. Well known is the ease with which excitement or other intense emotions can initiate vomiting. The common example is the child who cannot eat breakfast and vomits every morning before going to school. Many children will vomit if their food is not finely puréed, for the contact of a particle of food with the throat may set up a gagging mechanism. *Allergy*, however, is not a frequent cause of emesis in older children. If a child is intolerant of fat, he should be put on a high carbohydrate, low fat, low residue diet with small, frequent feedings.

Cyclic vomiting is most apt to occur in children with a *neuropathic background*, often brought to the front by an infection or an emotional complex.

An *infection*, although less often a cause of vomiting in older children than in the very young, may be a factor. Appendicitis, peritonitis, mesenteric adenitis, food poisoning, gastro-enteritis and meningitis must always be borne in mind as a cause of vomiting in children with an elevated temperature. Cerebral lesions such as brain tumor or abscess are uncommon as a cause of vomiting at this age.

DIARRHEA

The second great disorder of the intestinal tract of infants and children is diarrhea. If protracted, diarrhea is a very serious symptom, leading to dehydration with circulatory, cerebral, and renal symptoms which demand a restoration of fluid and electrolytes. In severe cases, a period of starvation for from twelve to twenty-four hours is necessary in order to rest the irritable intestinal tract. During this time parenteral

should excite suspicion of intestinal obstruction. If the obstruction is at the duodenum, vomitus with bile will generally be visible. There will be upper abdominal distention with a large gastric outline, and a visible, palpable duodenum, and an absence of stool. If the obstruction is lower, generally at the ileum, distention is more generalized, but the symptoms are similar. A flat film will reveal not only the obstruction but the site of the obstruction. Immediate surgery is indicated if the baby's life is to be saved. In capable hands, surgery results in recovery in 25 to 50 per cent of the cases.

Pylorospasm and *pyloric stenosis* are characterized by projectile vomiting, scant stools and loss of weight. If there is no response to medical treatment and if a mass in the pylorus is palpable, the case is one of pyloric stenosis and an operation should be performed as soon as possible to achieve the best results. Skipping from formula to formula will be of no avail; this is an organic disease of the stomach and not a mere dietary disorder. If the condition is that of simple pylorospasm, small, frequent concentrated feedings are indicated plus the administration of atropine, either by hypodermic or by mouth, twenty to thirty minutes after feedings. The dosage varies from $\frac{1}{1000}$ to $\frac{1}{200}$ grain, depending upon tolerance and need. The smallest effective dose should be used. Atropine fever and poisoning should be carefully watched for and the drug stopped at the first suggestion of drug toxicity. Sedation in the form of phenobarbital, $\frac{1}{8}$ grain four times daily, may also be used. Careful feeding—with the child fed and kept in a semisitting position, the body tilted to the right —is sometimes a helpful adjuvant. This position may also be of aid in functional vomiting.

In Older Infants:

In older infants the most common causes of vomiting are *overfeeding* and *infection*, and the remedy is reduction of the food intake. *Allergy* also may cause vomiting at this age. Cerebral infections such as meningitis may produce vomiting and for this reason must always be excluded in one's differential diagnosis; such disorders call for specific treatment as well as dietary changes. *Incomplete intestinal obstruction* of a con-

ticularly those of the hypertonic type, must be differentiated from true diarrhea. These movements are the result of an increased peristalsis of the hypertonic intestine and the stools are normal in appearance. For a short time one may view seven or eight normal stools daily without alarm and without resorting to a reduction of diet, for the number of stools spontaneously becomes normal in a few days.

Another type of frequent stool that must be differentiated from diarrhea is that of the starving baby. Due probably to hunger contractions, the starving baby's bowel movements are frequent but the yield consists only of a scant amount of mucus and intestinal secretions. There is no real stool. An analysis of the diet will reveal an extremely low caloric intake; the treatment is to increase and not decrease the food intake.

PARENTERAL DIARRHEAS.—Even if not enteric in nature, an infection may be a primary cause of diarrhea. Thus, a respiratory infection, particularly one of streptococcus origin such as otitis media, is very apt to cause diarrhea, *particularly in younger children*. Treatment consists mainly in caring for the primary infection and reducing the intake of food. Appendicitis and peritonitis in children may also produce diarrhea. Occasionally a proctitis is the causative agent; this may be infectious, sometimes gonorrheal, or it may be the result of contact with the diaper, with a resultant inflammation of chemical or bacterial nature. The proper sterilization of the diaper, with or without leaving the baby's diaper completely off until the inflammation subsides, will usually clear up the condition.

TREATMENT.—In general, the treatment of diarrhea is almost entirely dietary. The only drug which is specifically useful is sulfaguanidine in dysentery, 1 to 1½ grains per pound of body weight daily, in divided doses at intervals of four to six hours. Opiates are only for symptomatic relief in case of pain. Bismuth mixtures are of no genuine avail.

In Older Children:

In older children, the same factors are likely to produce diarrhea except that epidemic diarrhea does not occur and

fluid must be administered, preferably in the form of a continuous venoclysis of glucose and Ringer's or Hartman's solution. Feeding is restored very gradually, beginning with small amounts of diluted formula at frequent intervals, and increased only as the gastro-intestinal symptoms subside.

In the Newborn:

In the newborn, diarrhea is most serious. *Epidemic diarrhea* is a disease of unknown, insidious etiology attacking only newborn babies, and running through nurseries with a high mortality rate. The onset is with diarrhea, but loss of weight, fever, anorexia and vomiting follow rapidly. There is no blood in the stool. The children die either of secondary infection or from the alimentary intoxication caused by the uncontrolled diarrhea. The *treatment* is a sharp reduction of caloric intake with a formula of high protein, low fat, and low sugar content. If symptoms continue, starvation and parenteral fluids are in order.

Infectious diarrheas in the newborn are differentiated from epidemic diarrhea by the presence of inflammatory elements in the stool, namely, blood (usually) and mucus, and by the early onset of fever. Enteric organisms in the stool culture indicate diarrhea of the infectious or bacterial nature. The most commonly found organisms are the dysenteric and salmonella groups. Rare are the cases attributable to the Morgan bacillus and the Bacillus dispar. *In every case of persistent diarrhea, the stools must be repeatedly examined bacteriologically.*

The presence of blood and mucus in the stools of a newborn does not necessarily mean an infectious diarrhea. Just as the swallowing of an inordinate amount of fluid and detritus may initiate vomiting, so may it result in diarrhea accompanied by blood and mucus in the stool. Generalized visceral congestion due to asphyxia may cause blood to appear in the stools—the so-called blood in the normal stool of the newborn: Catharsis in the newborn may also cause bloody stools. And it must not be forgotten that overeating by infants as well as by children may cause transient diarrhea.

The frequent intestinal movements of some babies, par-

ticularly those of the hypertonic type, must be differentiated from true diarrhea. These movements are the result of an increased peristalsis of the hypertonic intestine and the stools are normal in appearance. For a short time one may view seven or eight normal stools daily without alarm and without resorting to a reduction of diet, for the number of stools spontaneously becomes normal in a few days.

Another type of frequent stool that must be differentiated from diarrhea is that of the starving baby. Due probably to hunger contractions, the starving baby's bowel movements are frequent but the yield consists only of a scant amount of mucus and intestinal secretions. There is no real stool. An analysis of the diet will reveal an extremely low caloric intake; the treatment is to increase and not decrease the food intake.

PARENTERAL DIARRHEAS.—Even if not enteric in nature, *an infection may be a primary cause of diarrhea*. Thus, a respiratory infection, particularly one of streptococcus origin such as otitis media, is very apt to cause diarrhea, *particularly in younger children*. Treatment consists mainly in caring for the primary infection and reducing the intake of food. Appendicitis and peritonitis in children may also produce diarrhea. Occasionally a proctitis is the causative agent; this may be infectious, sometimes gonorrheal, or it may be the result of contact with the diaper, with a resultant inflammation of chemical or bacterial nature. The proper sterilization of the diaper, with or without leaving the baby's diaper completely off until the inflammation subsides, will usually clear up the condition.

TREATMENT.—In general, the treatment of diarrhea is *almost entirely dietary*. The only drug which is specifically useful is sulfaguanidine in dysentery, 1 to 1½ grains per pound of body weight daily, in divided doses at intervals of four to six hours. Opiates are only for symptomatic relief in case of pain. Bismuth mixtures are of no genuine avail.

In Older Children:

In older children, the same factors are likely to produce diarrhea except that epidemic diarrhea does not occur and

parenteral infection has less effect. At this age there is also no diaper problem. Colitis, however, is more apt to occur in older children and is recognized by its protracted course and stubborn resistance to therapy. As in infants, older children can have the doubtful pleasure of diarrhea because of excessive fondness for food.

DIARRHEA CHARACTERIZED BY LARGE BULKY STOOLS

In the diarrhea caused by pancreatic deficiency and celiac disease, we have a form of diarrhea not infectious, not due to overeating, and not due to faulty diet, but due to an inability to digest or assimilate a normal diet. The stools are large, usually foul, and contain undigested elements with a high fat residue.

Diarrhea Due to Pancreatic Disease

It is only in recent years that we have come to recognize that infants may be born with pancreatic disease. If this is present at birth, the meconium may be so thick that obstruction results, usually in the ileum, and if unrecognized and not intelligently operated upon, death will result.

In early childhood, in spite of all measures, the baby has diarrhea and because of faulty fat digestion exhibits signs of vitamin A deficiency. Thus the keratinized bronchial epithelium may cause pulmonary atelectasis, and predispose to pneumonia and bronchiectasis. The symptoms of diarrhea and pulmonary disease of some duration in an infant who is marantic, in spite of good caloric intake, calls for an investigation of the pancreatic enzymes, by duodenal drainage or in the stool, and a study of vitamin A absorption into the blood.

TREATMENT.—When diagnosis is established, treatment is a *high protein and banana diet* with the oral administration of 5 grains three times daily of *pancreatic extract*, and *vitamins*. Thus a fatal disease can at times be averted. In milder cases, the children live but assume a form of indigestion difficult to distinguish from celiac disease but amenable to the same therapy of pancreatic extract and diet.

Diarrhea Due to Celiac Disease

Celiac disease occurs in the latter part of infancy some-what before or after a year of age. It is characterized by the marantic state, the distended belly, large, foul, greasy stools, grayish in color, signs of osteoporosis and rickets due to faulty absorption of fats and vitamin D. Glucose given by mouth results in little rise of the blood sugar, and x-ray study of the small intestine shows the segmentation, feathering and clumping, also seen in vitamin B deficiencies.

TREATMENT.—The cure of this disease is tedious and involves the expenditure of much time, taking months to years. Recent reports from the Harvard school have been most encouraging for, in addition to the usual *high protein and banana diet*, they administer large doses of *crude liver extract* and *vitamin B* parenterally. This is reported to ameliorate the faulty absorption which is reputed to be the basis of this disease. The results in restoring health have been better than customarily seen.

Diarrhea Due to Chronic Intestinal Indigestion

During the last decade I have seen a number of babies with symptoms suggesting the celiac syndrome or pancreatic insufficiency. These babies have large, frequent bowel movements, do not gain well, and have a diminishing appetite. This is a form of intestinal indigestion which, in these later years, seems to be definitely on the increase. A careful history almost invariably brings to light that these babies have been fed an extravagant diet in the early months of life. Not only cereal, but vegetables, eggs and even meat have been given at four or five months of age. This is an observation which has been confirmed by other pediatricians and bespeaks a definite danger in the sensational but ill-advised feeding of infants. This untoward feeding is a practice which should be condemned and can only be so condemned by repeated revelations of the disastrous consequences on the intestinal function in infant victims. It may be a long time before normal function is restored in these cases by the extreme limitation of fats and carbohydrates and the administration of large amounts of vitamins, which in some cases

have to be given parenterally. The *treatment* is the same as for celiac disease.

CONSTIPATION

One of the most frequent complaints of mothers about their children is constipation. As a threatening symptom it is much overrated, for with the exception of some underlying organic disturbance, such as obstruction, it seldom causes any harm. It is an obsession with most people that bowels must be moved every day at all costs. In the infant, constipation may be a cause of abdominal pain and crying on the act of defecation. Fissure in ano may result causing a film of blood outside the stool. While this is undesirable it does not cause fever and leads to no other sequelae. It is still a universal custom that the first home remedy when a child is taken ill is a cathartic, which cannot reach or cure the ill.

Diet is the most important factor in normal bowel movements. The bulk of the diet is an obvious requisite for proper intestinal stimulus. The small eater tends to be constipated; the big eater tends to move his bowels often. Protein is a constipating food, sugars and fats are laxative in nature, the starches are intermediate. It follows, therefore, that a proper protein-carbohydrate-fat ratio, together with bulk, is the important dietary bowel regulator. The different sugars also have more or less effect upon intestinal peristalsis. Lactose is most laxative, cane sugar next. Maltose and dextrin are most constipating. Vitamin B is also a definite bowel regulator. Therapeutically the whole B complex in large doses yields good results.

The infant's rectosigmoid region is characterized by a relatively sinuous course. This may be exaggerated by a long mesentery, leading to actual *kinking.* In such cases, no matter what is done, the constipation will be difficult to overcome. Fruit juices, purée vegetables and bulky cereals should be begun early so as to overcome a deficient gradient. In almost all cases the process of growth literally straightens out this intestinal anomaly until normal function eventually occurs. In rare cases, there is an actual stenosis of the sigmoid region which may lead to permanent constipation.

The *hypertonic* child as an infant may have either increased peristalsis or his hypertonicity may lead to spastic constipation. This form of imbalance of the autonomic nervous system may continue for years. Here dietary treatment is of no avail but drugs relaxing the vagotonic system may be effective. Atropine, physostigmine and more recently mecholyl may produce the desired results.

Aside from diet, the most important cause of constipation is *faulty habit formation*. The child never was interested to sit on the toilet seat, would deliberately refrain from and inhibit the act of evacuation. Thus, instead of the normal association having been formed of the proper time and proper place and proper act, the opposite effect has been obtained and perpetuated. If this is not corrected in short order by a judicious combination of firmness and happy association, the habit of constipation will have been formed. The administration of suppositories cannot play a curative role in such conditions. This can never be more than a temporary expedient, under any circumstances.

Not only is it important in cases of stubborn constipation to make certain of the normal anatomy of the bowel by means of barium enema and roentgen studies, but it is important, also, to make certain that there is no other organic cause for the constipation.

Cretinism will naturally make constipation difficult to cure if no thyroid is administered. *Cerebral conditions* such as idiocy and mental retardation also may make constipation a difficult problem. *Hirschsprung's disease* should be suspected when the constipation is very stubborn, if the abdomen becomes very distended, if a huge colon can be outlined, and if, when the stool is passed, it is tremendous. X-ray studies will confirm the diagnosis of megacolon. In recent years treatment of this disease has advanced so that, in addition to dietary treatment, mecholyl in dosage of 2 to 10 mg. is administered parenterally, and then later by mouth, 25 to 100 mg. In some instances operation (section) on the autonomic nervous system, sometimes with the addition of mecholyl, has yielded excellent results.

have to be given parenterally. The *treatment* is the same as for celiac disease.

CONSTIPATION

One of the most frequent complaints of mothers about their children is constipation. As a threatening symptom it is much overrated, for with the exception of some underlying organic disturbance, such as obstruction, it seldom causes any harm. It is an obsession with most people that bowels must be moved every day at all costs. In the infant, constipation may be a cause of abdominal pain and crying on the act of defecation. Fissure in ano may result causing a film of blood outside the stool. While this is undesirable it does not cause fever and leads to no other sequelae. It is still a universal custom that the first home remedy when a child is taken ill is a cathartic, which cannot reach or cure the ill.

Diet is the most important factor in normal bowel movements. The bulk of the diet is an obvious requisite for proper intestinal stimulus. The small eater tends to be constipated; the big eater tends to move his bowels often. Protein is a constipating food, sugars and fats are laxative in nature, the starches are intermediate. It follows, therefore, that a proper protein-carbohydrate-fat ratio, together with bulk, is the important dietary bowel regulator. The different sugars also have more or less effect upon intestinal peristalsis. Lactose is most laxative, cane sugar next. Maltose and dextrin are most constipating. Vitamin B is also a definite bowel regulator. Therapeutically the whole B complex in large doses yields good results.

The infant's rectosigmoid region is characterized by a relatively sinuous course. This may be exaggerated by a long mesentery, leading to actual *kinking.* In such cases, no matter what is done, the constipation will be difficult to overcome. Fruit juices, purée vegetables and bulky cereals should be begun early so as to overcome a deficient gradient. In almost all cases the process of growth literally straightens out this intestinal anomaly until normal function eventually occurs. In rare cases, there is an actual stenosis of the sigmoid region which may lead to permanent constipation.

In Older Children:

Like the colic of the infant, abdominal pain in older children is also a headache to the physician, who always fears that a surgical condition may be overlooked. When fever is present, appendicitis is always suspected. Food poisoning and enteric infections are characterized by abdominal pain, fever and diarrhea. Yet by far the most common cause (60 to 70 per cent) of abdominal pain in older children who are febrile is a *respiratory infection*. In these conditions, the lymphoid tissue of the intestinal tract and the mesenteric glands are involved and this is probably the cause of the abdominal pain. Operation in these cases is futile, and may be harmful. Certain neuropathic children, such as those with psychic vomiting, are also subject to abdominal pain, a form of enterospasm. This condition is aggravated by fever or emotional disturbances, and the treatment is sedation and the use of an antispasmodic. In cases without fever, abdominal pain according to the age calls for an exclusion of volvulus, intussusception, polyps, purpura and other medical conditions which may cause abdominal pain.

MELENA

The fifth large category of intestinal disturbances is the finding of blood in the stool. As previously pointed out, this may be a normal finding in the very early days of life; but if, in the first week of life, it is profuse, leading to anemia and accompanied by other signs of bleeding, the prothrombin time should be estimated. If this is very low, some form of vitamin K should be administered, first, 2 mg. parenterally and later in 1 mg. doses by mouth for a few days. This will cure hemorrhagic diseases of the newborn in short order.

Blood in a constipated stool due to a *fissure* has been previously mentioned. *Excessive catharsis*, particularly calomel, may produce bloody stools in a young infant. Finding of pure blood and mucus in the stool of an older infant with abdominal pain should make one suspect *intussusception*. A careful abdominal and rectal examination should be made, since surgery is indicated. *Meckel's diverticulum* with ulceration may be the cause of profuse hemorrhage in an infant or

ABDOMINAL PAIN AND COLIC

In the Infant:

There is nothing more distressing to both parents and doctor than a crying baby. When the cry is from pain such as colic, relief is demanded. Some causes of abdominal pain or colic have already been touched upon—such as pylorospasm, pyloric stenosis, the hypertonic baby with his hypertonic gastro-intestinal tract. The hungry baby swallows large amounts of air which cause flatulence and colic. The baby allergic to cow's milk suffers colic. Constipation with impacted feces is another cause of abdominal pain.

The true colic of infancy, which lasts through the first three to six months of the infant's life during which time the baby may cry almost incessantly, is a nerve-wracking disorder calling for patient understanding on the part of all concerned. Allergy often plays a role in these cases, and yet a resort to nonallergic diets seldom is a perfect solution. There is probably a constitutional disturbance of the gastrointestinal physiology due to an imbalance of the autonomic nervous system. Time corrects this balance, but no parent will calmly await the passage of months for a cure. *Sedatives* such as paregoric (3 minims for the young infant up to 10 minims for the infant of one year of age) and phenobarbital ($\frac{1}{10}$ grain for the very young infant up to $\frac{1}{4}$ grain at one year of age) should be used in goodly dosage, and *antispasmodics* of the atropine group may also be of value.

Careful technic in feeding the child, not overloading the stomach, avoiding air-swallowing, and favoring the semisitting position during and after feeding, are of distinct aid. Despite all these measures, this harmless disease is a source of great annoyance and headache to the doctor as well as to the patient.

In a pale child who suffers from colic and who has the habit of eating paint from toys or bedstead, *lead poisoning* should be suspected. Finding of a lead line in roentgenograms of long bones will confirm the diagnosis.

GASTRO-INTESTINAL ALLERGY*

AARON BROWN, M.D.†

and

FREDERICK R. BROWN, M.D.‡

THAT foods may produce various disturbances of the gastro-intestinal tract has been known since ancient days. In medical literature, as early as 1895, Osler[1] reported cases in which visceral crises were associated with urticaria and the confusion that arose between these cases and such surgical problems as intussusception, volvulus and renal colic.[2] In 1904, Morris[3] demonstrated edema of the gastric tissues obtained in lavaging the stomachs of patients with abdominal pain, nausea and vomiting. In 1909, Smith[4] demonstrated that the eating of buckwheat by his patient produced epigastric pain, nausea and vomiting.

Only in the last twenty years has serious attention been paid to allergy as a causative factor in these conditions.[5, 6, 7, 8, 9, 10, 11] It had been noticed that patients with asthma and hay fever often complained of gastro-intestinal symptoms and the deduction naturally followed that some of these symptoms might be due to allergy. During this period gastro-enterologists also noted that patients with abdominal complaints often had negative roentgen and laboratory findings and on further questioning and study, foods were revealed as the cause of these complaints.

An individual is said to be allergic if he reacts to a substance in a manner different from the ordinary or normal

* From the Department of Medicine, New York University College of Medicine and the Third Medical Division, Bellevue Hospital.

† Assistant Clinical Professor of Medicine, New York University College of Medicine; Assistant Visiting Physician, Third Medical Division, Bellevue Hospital.

‡ Assistant in Medicine, New York University College of Medicine; Clinical Assistant Visiting Physician, Third Medical Division, Bellevue Hospital.

a young child, with or without pain. The blood may be tarry or bright red. Surgery is indicated. X-rays are not of much use in diagnosing this condition.

Other causes of blood in the stool previously mentioned are dysentery, colitis, blood diseases such as purpura, and polyps. Sometimes tomato juice, beet juice and colored candy will simulate blood in the stools, causing needless alarm. Inspection of the stool, a direct question and chemical tests will prove that blood is not present. In a very young infant the urates and porphyrins of the urine will stain the diaper red when stool is present, and give a false impression of blood.

SUMMARY AND CONCLUSIONS

Three major points in the treatment of the common digestive disorders in infants and children have been emphasized, as follows:

1. Prevention by means of proper quantitative and qualitative diet, and proper feeding technic.

2. The treatment of digestive orders largely by means of dietary changes and proper fluid replacement, parenterally if need be.

3. Drugs play a small role in these diseases and the few that are useful have been mentioned.

The physician must always be on the alert for the surgical condition that occasionally occurs.

quently there is eosinophilic cellular infiltration of the tissues and in the secretions and excretions of the stomach and intestines.

Any food' or drug may produce manifestations in the gastro-intestinal tract. They act in several ways, first by direct contact and secondly by absorption and circulation through the blood stream, returning to the sensitive tissues in the gastro-intestinal tract and producing delayed reactions. The indirect reaction also occurs when constitutional symptoms follow overdosage in diagnosis or treatment of asthma and hay fever.

CLINICAL FEATURES

Allergy in humans, often called *atopy*, has certain characteristics and these are:

1. Sudden onset.
2. Attacks of short duration.
3. Abrupt cessation.
4. Periodicity—the most important characteristic.
5. A family history of allergy in over half the cases.
6. Eosinophilia in the blood and tissues.
7. A favorable response to injections of epinephrine.
8. Positive skin reactions in about half the cases.

Gastro-intestinal symptoms that follow some of the above criteria, especially if they occur in persons with a family or personal history of other allergies such as hay fever or asthma, should be investigated for a possible allergic basis. It is of course imperative to exclude organic disease of the gastro-intestinal tract by appropriate roentgen and laboratory investigation.

REGIONAL GASTRO-INTESTINAL MANIFESTATIONS

Gastro-intestinal manifestations of allergy are more commonly associated with the presence of other allergic symptoms and only infrequently occur as isolated symptoms. While any individual may present symptoms suggesting involvement of one or more parts of the gastro-intestinal tract or its appendages, it is best to consider the manifestations of gastro-intestinal allergy along anatomic lines.

person. Thus, to most of us, eggs, milk and wheat are harmless and wholesome foods, yet in a small percentage of individuals even a small amount of these foods may produce alarming symptoms. Such individuals are normal in every other respect, except for this peculiarity or idiosyncrasy.

Allergy requiring medical consultation affects almost 10 per cent of the population, but of this group the number requiring attention for gastro-intestinal symptoms is not large. Gastro-intestinal allergy is more frequent in infants and children, reflecting their greater susceptibility to food sensitivity.

PATHOGENESIS

All allergic patients have a *threshold of sensitivity*. It requires exposure to a certain amount of a substance to which a person is sensitive before symptoms ensue. This threshold tends to vary in different individuals. Once this threshold of protection is exceeded, symptoms follow and thereafter less and less of the offending substance is necessary to evoke further attacks. Thus, some of our patients may eat one egg without trouble but two eggs would produce urticaria and dyspeptic symptoms. Sometimes an exceedingly small amount of food can provoke symptoms. This threshold may be altered by emotional states, and frequently tension and worry will lower the threshold so that smaller quantities of offending foods will induce symptoms. The threshold may also be lowered by ingestion of alcohol. Sometimes combinations of foods will call forth symptoms when similar quantities of these foods taken alone are tolerated.

The site of allergic reactions depends on the presence of antibodies in the tissues, such tissue being known as *shock tissue*. When shock tissue exists in the organs of the gastrointestinal tract, contact of the offending foods with antibodies located in these organs results in the allergic reaction. This reaction is characterized by edema producing swellings similar to urticarial wheals and secondarily by associated muscle spasm. The latter results in changes in tonicity and motility of the small and large bowel. More severe reactions show evidence of increased vascular permeability in the appearance of mucosal and submucosal hemorrhages, and fre-

spasm and *pylorospasm*[13] may be due to allergy. It is imperative to rule out all organic lesions by roentgen study, gastric analysis, etc., in these cases.

CASE III.—G. M., a man aged thirty-three years, was a hay fever patient who complained of a bad taste in his mouth, heartburn, a feeling of depression and diarrhea for three years. These symptoms occurred periodically with free intervals of a week or longer. He was investigated and treated by a gastro-enterologist for some time without relief. He suspected asparagus, roast beef, eggs and apple as being responsible for this condition. Tests showed him to be skin sensitive to ragweed, house dust, peas, beans, egg, chocolate, apple, crab and lobster. Following exclusion of the foods from his diet, his symptoms disappeared and he gained 20 pounds in several months.

Ulcer-like Symptoms.—The peptic ulcer syndrome may be simulated in allergic individuals. Repeated roentgen examination will often show niches in different locations suggesting temporary mucosal swellings. This type of case is often associated with urticaria and angioneurotic edema.

CASE IV.—L. G., a physician aged thirty-five years, was treated for hay fever for several years and gave the history that recently he suffered from heartburn and epigastric distress one to one and a half hours after meals. The symptoms responded somewhat to alkalies and food. Gastro-intestinal fluoroscopy gave negative results. He suspected wheat as the cause of his trouble and upon elimination of wheat his symptoms stopped. A short time later the same symptoms recurred and he traced it to a sauce containing flour. He can take pure rye bread without trouble but rye bread containing wheat induces symptoms. His skin test to wheat had changed from negative before these symptoms arose to positive after the onset of symptoms.

Rinkel[14] reported a patient who had five operations for duodenal ulcer with return of symptoms after each operation. The symptoms were later found to be due to ingestion of milk, wheat and eggs.

Ehrenfeld, Brown and Sturtevant[15] found a small group among allergic patients who had ulcer-like symptoms but on

Oral Region

Cheilitis, an inflammation of the lips, often with cracking and blistering, is frequently due to foods such as cinnamon, eggs, milk and fish.

Herpes labialis may be an expression of food allergy, since it is not infrequently found with other signs of gastro-intestinal allergy.

Canker sores and *white patches* in the mouth are frequently due to foods and drugs, especially mouth washes and cinnamon.

Stomatitis and swelling of the buccal mucous membrane and tongue may occur as an isolated manifestation of allergy, but more frequently they are associated with angioneurotic edema due to foods and drugs especially eggs, milk, fish and aspirin.

CASE I.—I. S., a boy eight years of age, had a history of asthma due to rabbit hair which cleared up when the source of the rabbit hair was found and eliminated. His mother reported that the child suffered from repeated swellings of the lips and tongue. Tests showed him to be sensitive to egg and elimination of egg from his diet stopped further symptoms.

CASE II.—A. R., a man sixty-two years old, complained of swelling of the mouth and tongue of five months' duration. He suspected fish because his first attack came in Florida after eating fish. Skin tests for fish were negative as were all food tests but on elimination of fish from his diet, all symptoms disappeared.

Esophagus

Dysphagia, sensation of constriction in passage of food after swallowing and *globus hystericus* suggest reactions in the esophagus. Withers[12] recently reported a case with symptoms suggesting involvement of the esophagus and trial diets incriminated string bean, peanut, sardine and chocolate.

Stomach

Here a variety of symptoms are complained of: these include *distention, heartburn, epigastric distress, anorexia, epigastric pain, nausea* and *vomiting*. The symptoms of *cardio-*

spasm and *pylorospasm*[13] may be due to allergy. It is imperative to rule out all organic lesions by roentgen study, gastric analysis, etc., in these cases.

CASE III.—G. M., a man aged thirty-three years, was a hay fever patient who complained of a bad taste in his mouth, heartburn, a feeling of depression and diarrhea for three years. These symptoms occurred periodically with free intervals of a week or longer. He was investigated and treated by a gastro-enterologist for some time without relief. He suspected asparagus, roast beef, eggs and apple as being responsible for this condition. Tests showed him to be skin sensitive to ragweed, house dust, peas, beans, egg, chocolate, apple, crab and lobster. Following exclusion of the foods from his diet, his symptoms disappeared and he gained 20 pounds in several months.

Ulcer-like Symptoms.—The peptic ulcer syndrome may be simulated in allergic individuals. Repeated roentgen examination will often show niches in different locations suggesting temporary mucosal swellings. This type of case is often associated with urticaria and angioneurotic edema.

CASE IV.—L. G., a physician aged thirty-five years, was treated for hay fever for several years and gave the history that recently he suffered from heartburn and epigastric distress one to one and a half hours after meals. The symptoms responded somewhat to alkalies and food. Gastro-intestinal fluoroscopy gave negative results. He suspected wheat as the cause of his trouble and upon elimination of wheat his symptoms stopped. A short time later the same symptoms recurred and he traced it to a sauce containing flour. He can take pure rye bread without trouble but rye bread containing wheat induces symptoms. His skin test to wheat had changed from negative before these symptoms arose to positive after the onset of symptoms.

Rinkel[14] reported a patient who had five operations for duodenal ulcer with return of symptoms after each operation. The symptoms were later found to be due to ingestion of milk, wheat and eggs.

Ehrenfeld, Brown and Sturtevant[15] found a small group among allergic patients who had ulcer-like symptoms but on

complete gastro-intestinal investigation had no demonstrable roentgen signs of ulcer. There were spastic phenomena in the stomach or duodenum or both in each of these cases and this group showed a striking, though not constant, association with urticaria and angioneurotic edema.

Holmes[16] recently reported that seven out of seventy-five patients with peptic ulcers showed gastro-intestinal allergy and that this type of case cleared up only after abstention from the offending food.

Small and Large Intestine; Biliary System

Mucous and Ulcerative Colitis.—When the site of the allergic reaction is in the small and large bowel, there is frequently abdominal pain, tenesmus, constipation, diarrhea and bleeding. This type frequently produces well defined syndromes, such as mucous colitis in the milder cases and chronic ulcerative colitis in the more severe ones.[17] In ulcerative colitis an estimate of food sensitivity should be made before radical surgery is resorted to.[18, 19] There have been reports of mucous colitis being due to specific foods with clearing of symptoms upon elimination of these foods.[20] Undoubtedly there is also a considerable neurogenic factor in the causation of mucous colitis.[21]

Case V.—J. C. M., a twenty-two-year-old medical student, was a thin, emaciated individual complaining of attacks of diarrhea lasting a week or more and recurring every few weeks. He had lost 20 pounds in the past year. His family history was positive for allergy and he had an associated asthma. Gastro-intestinal investigation was negative. He was aware of a food idiosyncrasy and knew he could not take eggs. Skin tests were positive for egg and he gave a marked reaction to almond. He always suspected chocolate but did not react to this substance. Further questioning revealed he continually indulged in chocolate almonds and when he switched to plain chocolate his symptoms disappeared and he gained 30 pounds in the next year.

Appendicitis Syndrome.—There have been many reports in the literature of acute abdominal pain often localizing in the right lower quadrant accompanied by nausea and vomit-

ing caused by food allergy.[5, 22, 23, 24] This type of case often is diagnosed as acute appendicitis since fever and leukocytosis may occur and these patients frequently come to operation. After the operation the symptoms often recurred. Further investigation often revealed the presence of food allergy.

Intestinal Obstruction.—In angioneurotic edema of the intestine, symptoms may simulate acute intestinal obstruction. Gallison[25] reports a case of partial intestinal obstruction in a twenty-nine-year-old male who had five previous attacks. The attacks were relieved by adrenalin but then recurred. Skin tests revealed positive reactions to prune and egg and elimination of these foods resulted in freedom from symptoms for one month. The etiologic factor was proved when further ingestion of these foods resulted in an acute attack of pain, nausea, vomiting and diarrhea.

Idiopathic Bleeding.—Lintz[26] in 1924 found that eighteen of forty-four asthmatic patients showed microscopic blood in the gastric contents and sixteen of twenty-five asthmatics showed blood in the feces. It is not inconceivable that the more severe gastro-intestinal reactions to food may result in macroscopic bleeding. This is more frequent in the lower bowel.

Henoch's Purpura.—This syndrome is not infrequently a manifestation of sensitivity to foods or drugs, especially the latter.

Pruritus Ani.—Pruritus ani, either isolated or accompanying a generalized pruritus or in association with other gastrointestinal symptoms has been shown to be due to food allergy in many instances and elimination of the offending foods frequently results in cessation of the itching.

Pseudocholecystitis.—Alvarez[27] has reported on a series of patients with syndromes suggesting gallbladder disease who were operated upon without obtaining relief until the foods to which the patients were sensitive were found and eliminated.

Gastro-Intestinal Symptoms due to Pollen.—During the hay fever season, patients suffering from this disease sometimes complain of abdominal pain and diarrhea. We believe these symptoms are due to the ingestion of pollen and in the

oral treatment of pollenosis where the pollen dosage is taken in the form of enteric-coated tablets, these symptoms have been noted more frequently. When a general reaction occurs in a patient receiving injection treatment for hay fever, it occasionally takes the form of nausea and abdominal cramps as well as coryza, asthma and urticaria. This is probably due to an urticarial reaction or local edema occurring in the intestinal tract.

Infants and Children

Gastro-intestinal manifestations of allergy occur more often in children than in adults and are usually associated with other allergic conditions. Sometimes they are the earliest allergic symptom to appear. When the family history is positive on both sides, the symptoms tend to manifest themselves earlier.

Often initial contact with a food such as milk, orange, or egg may result in *swelling* of the lips, mouth or tongue, *abdominal cramps, vomiting* or *diarrhea*. It has been shown that unaltered food protein occurs in breast milk[28] and symptoms may start while the child is still on breast feeding without the addition of new foods. The reactions in children are often violent, projectile vomiting being frequent. Symptoms suggestive of hypertrophic pyloric stenosis with the failure to find any pathologic process at operation have been found in infants who later showed definite food hypersensitivity.[29]

Other infants may tolerate breast feeding quite well yet when cow's milk is added to the diet, colic or other gastrointestinal symptoms may result. An infant is easy to study from the point of view of food allergy inasmuch as foods are added to the diet one by one usually and the onset of symptoms coincidental with the addition of a new food frequently makes the intelligent mother aware of the child's intolerance for that food. However, symptoms sometimes do not begin until a child has been on a food for some time.[30] *Poor appetite* and *persistent refusal of a food substance* by a child should make one suspicious of food allergy.

Case VI.—L. B. was four years old. Her father had fall hay fever. The history revealed vomiting spells and diarrhea for a

week at a time for one year. Skin tests revealed sensitivity to rye, cinnamon, cloves, beet, mushroom, tomato, sweet corn, coconut, peach, prune, cheese and peppermint. On exclusion of these foods from her diet, she has remained symptom free to date.

In older children, recurrent attacks of vomiting with intervals of freedom from symptoms, so-called *cyclic vomiting*,[29, 30, 31, 32] has been regarded by many as a manifestation of food allergy. A careful food history is important in these children, since skin tests are often of limited value. A history of previous eczema or of associated allergic disease is often obtained in these patients.

DIAGNOSIS

As with asthma and hay fever, we depend on the following for a diagnosis:

1. A complete and careful history with special reference to family and personal history of allergy; periodicity of symptoms; food likes and dislikes; overindulgence in certain foods; changes in diet habits; recurrence of symptoms on certain days of the week.
2. Skin tests—scratch or intracutaneous.
3. Trial diets, exclusion diets, addition diets, food diaries, etc.

It must be stressed that all efforts should be made to rule out the presence of organic disease of the gastro-intestinal tract when gastro-intestinal symptoms are complained of. It should include *roentgen studies* of the entire tract and other indicated laboratory work. Allergy should be suspected when any of the following points are present: a positive family *history* of allergy; a personal history of allergy; history of food dislikes; positive skin reactions; definite *clinical symptoms* relating to the ingestion of food as shown by food diaries or exclusion diets. Roentgen findings of hypermotility or hypertonicity should make one suspect allergy.[33] *Skin testing* is more valuable in children and in patients with other atopic conditions. Our most important aid in the diagnosis of gastro-intestinal allergy is a study of the *diet*. There are various ways of doing this, the most important being food diaries, addition diets and elimination diets.

History

As an etiologic factor *heredity* plays a part, over half the cases of gastro-intestinal allergy giving a positive family history of allergy. The general rule is that the greater the inherited factor, the earlier is the age of onset of symptoms.

Skin Tests

We can dismiss skin tests as being of limited value. A positive skin reaction may mean (1) that the substance has previously caused symptoms but no longer is clinically important; (2) that it is responsible for symptoms at the time of testing. (3) A reaction limited to the skin which may denote potential trouble, especially important in infants and children.

When symptoms follow within a half hour or thereabouts following the ingestion of food, the intelligent person may usually discover the cause of his symptoms. Here the skin reaction is frequently positive and confirmatory. When many skin reactions are positive, some are highly significant as etiologic factors and others are of little importance. In these cases dietary study is more important.

Skin testing *extracts* are made from raw foods, whereas cooking and digestion often change the food eaten. Thus the patient with negative skin reactions may actually be sensitive to some product of digestion, rather than to the original food protein. Testing with extracts of cooked foods has given us fewer positive skin reactions than with those extracted from raw foods. Some food extracts, notably fruits, lose their potency very rapidly and this may also explain negative skin reactions. When there is an associated respiratory or other allergy, skin tests may be of considerable value.

Food Diaries

A food diary is a record of every food substance or ingested medication taken over a period of time, usually a month or longer, while at the same time a notation of the appearance or aggravation of symptoms is made. By noting the temporal relationship between the gastro-intestinal symptoms and the ingestion of certain substances, the etiologic factor or

factors may be discovered. This correlation should occur several times and should be checked up by direct testing of the

EXAMPLE OF FOOD DIARY:

Name...E.C.B...... Period from 1/7/38 to 2/24/38		X - Food taken O - Symptoms
Upper square 7AM-12M; Middle square 12M -7PM; Lower square 7PM-7AM		

Fig. 138.—Example of food diary.

suspected food or drug taken by mouth. We must insist that during the period of recording, only simple foods be taken

excluding such dishes as hashes, stews and vegetable soups, all of which contain numerous items.

The accompanying example (Fig. 138) is the chart of a patient with epigastric distress who was advised to simplify his diet while recording it. You will note that his symptoms abated on January 14 when the following foods were absent from the diet: milk, chocolate, beef, tomato, peas, carrot, apple, lettuce and pork. Symptoms recurred a few days later when milk, chocolate, carrot, apple and lettuce and tomato were resumed. Symptoms again disappeared when milk was eliminated and the record for two months reveals symptoms whenever milk was resumed in the diet. The resumption of chocolate, beef, tomato, pea, carrot, apple and lettuce did not provoke symptoms. Whenever pork in any form was taken, symptoms resulted shortly thereafter. After the elimination of milk and pork, based upon the results of this dietary study for two months, complete relief from epigastric distress resulted. The addition of other food substances not on the illustrated list did not provoke further attacks. It will be noted that milk and pork ingestion was tried on several occasions, but it always resulted in distress.

Addition Diet

The addition diet is valuable for persons who are not actively working or who are hospitalized. The ideal start would be to starve the patient for several days, giving nothing by mouth except water, and then adding foods one by one at one- to two-day intervals. If symptoms do not disappear during the starvation period, it is unlikely that foods are the cause of the symptoms and dietary rearrangement probably will not be effective.[34] As foods are added one by one, the return of any of the symptoms should make one suspicious of that food. It should then be eliminated and tried again after a period of time in order to make sure that it is the food or one of the foods responsible for symptoms. In this way, over a period of time, one is able to arrive at a diet which keeps the patient free of symptoms. The choice of foods to be added to the diet first should be those which uncommonly are responsible for symptoms, so that a nutritious sustaining diet

can be arrived at early. If you do not wish to starve the patient, a basal ration of lamb, rice, butter, sugar and water[34] can be used to start with, adding foods one by one after symptoms have diminished or disappeared.

Elimination Diets; Other Diagnostic Measures

The third type of dietary study, *elimination diets* as advocated by Rowe,[35] which first eliminate an important food or group of foods and later may consist of milk alone, has not been as useful in our hands as the other two types of dietary study.

In 1934, Vaughn[36] suggested the *leukopenic index* as useful in the diagnosis of food allergy. He considered that allergic sensitivity to a food exists if ingestion of the food is followed by a significant fall in the total leukocyte count of 1000 to 2000 cells. This test is not considered significant; even in 1933 Simpson[37] stated that leukocyte counts of healthy people vary continually and even when the counts are taken minutes apart.

The presence of blood *eosinophilia* is suggestive of allergy but in the gastro-intestinal cases it is infrequently found. More suggestive and helpful is the finding of eosinophils in secretions obtained at stool or by sigmoidoscopy.

In general, *roentgen findings* are usually negative but hypermotility, hypertonicity and spastic phenomena may be found. When a migratory niche is found in repeated gastro-intestinal x-ray series, it is suggestive of mucosal edema and gastro-intestinal allergy.

The *erythrocyte sedimentation rate* in allergy is usually normal. This determination should be made to rule out neoplasms or infection as the cause of the symptoms.

Confirmatory evidence of gastro-intestinal food allergy was obtained by Thomas and Renshaw[38] by placing dried allergens directly on the *rectal mucosa*. They then observed the test sites by proctoscopy and obtained evidence of positive reactions.

A majority of patients with gastro-intestinal allergy are seen by gastro-enterologists and here the diagnosis is one of *exclusion*. Those patients usually seen first by the allergist are

the ones who have gastro-intestinal symptoms in addition to other allergic manifestations. This group is the one that more frequently shows positive skin reactions.

TREATMENT

The treatment of gastro-intestinal allergy due to foods or drugs is *the elimination of the offending foods and drugs*. The patient must be instructed as to the occurrence of the offending food substance in the more complex foods, such as egg in sponge cake. Complete elimination of one or two foods is easy but when many food factors are found there may be some difficulty in arranging a nourishing and pleasing diet. It is important to arrange substitutes for essential foods. When infants and children are sensitive to cow's milk, one should try goat's milk, superheated milk or soy bean preparations.

In those patients who show many positive skin reactions, the elimination of all the possible factors responsible for symptoms may lead to malnutrition. It is important here to test and retest the food factors by direct ingestion during periods of freedom from symptoms so that the best possible diet can be arrived at. It is important to explain the significance of positive skin reactions to the patient in order to guard against falsely accusing a food in the suggestible type of patient. We are all familiar with the food faddist who decide almost everything they eat causes symptoms and so have restricted their diets as to produced nutrititional edema and vitamin deficiencies. How often the patient complains that all meats bother him, that all green vegetables cannot be tolerated, that he cannot eat fresh fruits! In this day of dietary consciousness, the physician should not allow himself to be the factor responsible for malnutrition.

When the diet has been arranged, it is important to estimate whether suitable sources of vitamins and minerals are present; if they are not, the diet should be supplemented by the numerous preparations of these substances that are now available.

The elimination of foods is not a permanent curtailment of the diet. It has been noted that a patient's tolerance for a food

may return after that food has been absent from the diet for six months to several years. The physician L.G., (Case IV) mentioned previously, has found that he can now tolerate wheat after omitting it for four months. In general, *dietary trial* is the essential test of return of tolerance to foods and it is not necessary to resort to the skin testing procedures.

An allergic individual has the tendency to develop sensitivities and this tendency remains throughout his life. There is no reason why the elimination of offending foods should prevent further sensitivity to other foods from developing and this must be expected in our allergic individuals. However, once we have made a complete investigation, it is easier to find out new factors which may arise at any time. Of course we must remember that the allergic individual is just as susceptible to organic diseases as the normal person.

It is imperative to institute therapy for the associated allergic conditions that may be present, for we cannot expect good results in treatment of gastro-intestinal allergy by merely picking out one phase of sensitivity to treat.

There have been many reports of oral and injection methods for *desensitizing* food allergic individuals. Unless a food is essential to life and a substitute possessing all its nutritive aspects is not available, however, it is not necessary to resort to them. We have treated allergy due to milk, egg, wheat and oranges by both oral and injection methods of desensitization. We start with small doses and increase the amount given at regular intervals. These methods ordinarily do not restore the full tolerance of an individual for any food but treated patients have been able to tolerate as much as a half glass of milk several times daily and several slices of wheat toast.

For control of symptoms by medical means, we have found *antispasmodics* and *dilute hydrochloric acid* of some use. Some patients can be well controlled by *ephedrine sulfate*. We have not found *epinephrine* particularly effective in reducing acute symptoms nor has it been useful as a diagnostic aid in differentiating those attacks of food allergy simulating an acute abdominal condition from organic diseases, as we have been led to believe from previous reports.

SUMMARY

1. Gastro-intestinal symptoms may be due to food or drug allergy.

2. These symptoms may simulate organic diseases of the gastro-intestinal tract and its appendages.

3. Careful study of past history and diets are essential for diagnosis.

4. It is imperative to rule out organic disease by laboratory studies.

5. Treatment is essentially the elimination of the offending food or drug and control of associated allergic conditions.

BIBLIOGRAPHY

1. Osler, W.: On the Visceral Complications of Erythema Exudativum Multiforme. Am. J. M. Sc., *110*: 629, 1895.
2. Osler, W.: On the Surgical Importance of the Visceral Crises in the Erythema Group of Skin Diseases. Am. J. M. Sc., *127*: 751, 1904.
3. Morris, R. S.: Angioneurotic Edema. Am. J. M. Sc., *128*: 812, 1904.
4. Smith, H. C.: Buckwheat Poisoning. Arch. Int. Med., *3*: 350, 1909.
5. Duke, W. W.: Food Allergy as a Cause of Abdominal Pain. Arch. Int. Med., *28*: 151, 1921.
6. Rowe, A. H.: Gastro-intestinal Allergy. J.A.M.A., 97: 1440, 1931.
7. Rowe, A. H.: Food Allergy in the Differential Diagnosis of Abdominal Symptoms. Am. J. M. Sc., *183*: 529, 1932.
8. Cooke, R. A.: Gastro-intestinal Manifestations of Allergy. Bull. New York Acad. Med., *9*: 15, 1933.
9. Vaughn, W. T.: Food Idiosyncrasy as a Factor of Importance in Gastro-enterology and in Allergy. Rev. Gastro-enterol., *5*: 1, 1938.
10. Collins, E. N. and Pritchett, C. P.: Allergy as a Factor in Disturbances of the Gastro-intestinal Tract. M. CLIN. NORTH AMER., *22*: 297, 1938.
11. Andresen, A. F. R.: Gastro-intestinal Allergy. Its Present Status. South. M. J., *34*: 418, 1941.
12. Withers, O. R.: Gastro-intestinal Allergy with Special Reference to the Esophagus. South. M. J., *32*: 838, 1939.
13. Balyeat, R. M. and Pounders, C. M.: Pylorospasm due to Allergy. South. M. J., *26*: 436, 1933.
14. Rinkel, H. J.: Gastro-intestinal Allergy. II. Concerning the Mimicry of the Peptic Ulcer Syndrome by the Symptoms of Food Allergy. South. M. J., *27*: 630, 1934.
15. Ehrenfeld, I., Brown, A. and Sturtevant, M.: Studies in Gastro-intestinal Allergy. Allergy in the Pathogenesis of Peptic Ulcer. J. Allergy, *10*: 542, 1939.
16. Holmes, G.: Analysis of Some Cases of Gastro-intestinal Allergy Associated with Organic Diseases. South. M. J., *34*: 634, 1941.
17. Andresen, A. F. R.: The Surgeon and Colonic Allergy. Am. J. Surg., *50*: 281, 1940.

18. Phillips, C. E.: Cecostomy for Allergic Colitis. S. Clin. North Amer., 11: 1117, 1931.
19. Mackie, T. T.: The Medical Management of Chronic Ulcerative Colitis. J.A.M.A., 111: 2071, 1938.
20. Hollander, E.: Mucous Colitis Due to Food Allergy. Am. J. M. Sc., 174: 495, 1927.
21. Bockus, H. L., Bank. L. and Wilkinson, S. A.: Neurogenic Mucous Colitis. Am. J. M. Sc., 176: 813, 1928.
22. Duke, W. W.: Allergy as a Cause of Gastro-intestinal Disorder. South. M. J., 24: 363, 1931.
23. Lintz, W.: Appendicitis in 300 Cases of Asthma and Other Forms of Allergy. New York State J. Med., 25: 369, 1925.
24. Lieberman, D. L.: The Appendicitis Syndrome due to Food Allergy. Connecticut M. J., 5: 277, 1941.
25. Gallison, D. T.: Gastro-intestinal Allergy as a Cause of Intestinal Obstruction. New England J. Med., 211: 164, 1934.
26. Lintz, W.: Gastro-intestinal Bleeding in Asthma and Other Forms of Allergy. Boston M. & S. J., 190: 980, 1924.
27. Alvarez, W. C.: "Pseudocholecystitis" Apparently Caused by Food Sensitiveness. Proc. Staff Meet. Mayo Clin., 9: 680, 1934.
28. Donnally, H. H.: The Question of Elimination of Foreign Protein (Egg White) in Woman's Milk. J. Allergy. 1: 78, 1929.
29. Casparis, H.: Gastro-intestinal Allergy in Children. Ann. Int. Med., 7: 625, 1933.
30. Fries, J. H. and Zizmor, J.: Gastro-intestinal Allergy in Children. J. Pediat., 16: 69, 1940.
31. Tallerman, K. H.: Recurrent Vomiting Attacks in Childhood with Special Reference to Allergic Factors. Brit. M. J., 2: 766, 1934.
32. Hinnant, I. M. and Halpin, L. J.: Food Allergy in Mild and Severe Cyclic Vomiting. Med. Clin. North Amer., 19: 1931, 1936.
33. Fries, J. H. and Zizmor, J.: Roentgen Studies of Children with Alimentary Disturbances due to Food Allergy. Am. J. Dis. Child., 54: 1239, 1937.
34. Alvarez, W. C.: Ways of Discovering Foods that are Causing Indigestion. Proc. Staff Meet., Mayo Clin., 12: 88, 1937.
35. Rowe, A. H.: Clinical Allergy. Lea & Febiger, Philadelphia, 1937.
36. Vaughn, W. T.: Food Allergens; Leucopenic Index; Preliminary Report. J. Allergy, 5: 601, 1934.
37. Simpson, R. H.: Physiological Leucocyte Counts and the Detection of Small Variations from the Normal. Brit. J. Radiol., 6: 705, 1933.
38. Thomas, J. W. and Renshaw, R. J. F.: Gastro-intestinal Allergy: Proctoscopic Observation. South. M. J., 34: 528, 1941.

THE SWEDISH HOSPITAL

DIAGNOSTIC PITFALLS IN RECTOCOLONIC DISEASE

F. M. FRANKFELDT, M.D.*

THE teaching of the subject of rectocolonic diseases in medical colleges is generally inadequate, and few hospitals are staffed with a well trained proctologist, hence the average doctor embarks on a medical career without the opportunity of familiarizing himself with methods of diagnosis in this important field. Is it any wonder that pathologic conditions in the rectum and colon are either overlooked or treated without any attempt at scientific investigation? Early diagnosis is imperative, otherwise apparently simple conditions become progressively worse, less responsive to treatment and may even threaten the patient's life.

By utilizing a routine procedure the error quotient in diagnosis can be reduced to a minimum. Such a routine is indicated in the headings which follow.

HISTORY

A carefully taken history is of immeasurable importance.

FAMILY HISTORY.—Inquire as to a possible background of tuberculosis, malignancy, multiple polyposis, hemorrhoids, allergy, or eczema.

PREVIOUS HISTORY.—*Surgical:* Has the patient ever been operated on, and did the condition for which operation was done have any relationship to the present complaint? *Medical:* Has he ever suffered from allergy, eczema, ringworm, seborrhea of scalp, venereal disease, dysentery? Has he used sedative drugs or cathartics particularly of the anthracene group? *Menstrual Complaints:* Inquire as to their relationship to bowel symptoms. *Urinary disturbances.*

---

* Proctologist, Bronx Hospital.

Present History.—Is this the first attack? Was the onset sudden or insidious?

Pain: Location, type, duration, relationship to defecation. Differentiate between pruritus and pain.

Bleeding: Color, quantity, frequency, occurring with or without "going to stool."

Constipation and Diarrhea: A sudden change of bowel habit is one of the first symptoms of malignancy. How many stools a day, type, color, shape, odor, whether or not mixed with blood, mucus, or pus?

Protrusions: Type, shape, are they reducible, are they accompanied by bleeding or pain?

Constitutional Symptoms: Cough, nights sweats, wasting, asthenia, diabetes, gout, arthritis.

Laboratory Findings: If findings are positive, determine their relationship to present complaint.

GENERAL PHYSICAL EXAMINATION

Observe posture (mendicant's posture occurs in severe chronic ulcerative colitis), gait, manner of sitting down. Examine scalp for seborrhea, ears for eczema, tongue for vitamin B deficiency, skin for eczema, ringworm, urticaria, psoriasis; thyroid, eyegrounds; estimate blood pressure; examine heart and lungs including x-ray; look for anemia, jaundice, evidence of wasting.

Examination of Abdomen.—Diastasis recti with lax abdominal wall will explain ptosis. *Ascites* may be due to decompensated heart and kidneys, hepatic cirrhosis, or malignancy with peritoneal involvement. If a *mass* is felt in the cecal region consider tuberculosis, malignancy, or nonspecific granuloma with distal ileitis. A tumor in the sigmoid region is suggestive of diverticulitis with or without abscess, or of malignancy. If the mass is of doughy consistency it is probably due to impacted feces. In psychoneurotics these portions of the colon are unusually sensitive to palpation. Examine for pathologic change in the liver, spleen and kidneys. Palpate the inguinal glands. The anterior chain drains the perianal region and changes in that area will show corresponding disease in these glands. Enlarged or abscessed glands warrant laboratory tests—Wassermann test, Frei test, biopsy.

INSPECTION OF ANUS, RECTUM AND COLON

The patient assumes the left lateral prone position with knees well flexed on the abdomen. A focusing type of floor lamp furnishes excellent illumination.

Do not overlook postanal dimples (two or more small fistulous openings in integument over the lower sacral region, with hairs frequently protruding from these sinuses). They indicate a *pilonidal cyst*. This may be abscessed or an external fistulous opening may be encountered 2 or 3 inches from the midline which communicates with the cyst.

An inflammatory process involving an entire buttock, the integument a dusky red or blackish hue, with evidence of crepitation, is presumptive evidence of a *gas bacillus infection*. The patient looks acutely ill, is toxic and the condition requires prompt and energetic therapy.

The external opening of a *fistulous tract* may be found anywhere in the perianal region. If one draws an imaginary line between the ischial tuberosities, the anal outlet is divided into an anterior and posterior part. If the external opening is located posterior to this line the internal opening will be found in the posterior commissure between the external and internal sphincters; if the external opening is anterior to this line. the internal opening will be found directly inward.

By separating the buttocks the perianal region is well exposed. *Skin* in this location may be acutely inflamed, red, edematous, excoriated and exude a considerable amount of serum. There may be vesication, desquamation, thickening, pigmentation, loss of pigment and the integument may be thrown into radiating folds. The skin is often found to be thin and dry, and to crack easily and bleed on the slightest attempt at stretching. If such skin lesions exist, with a well defined lateral border plus a history of seborrhea or ringworm particularly of the interdigital type (athlete's foot), suspect the process to be of fungous origin. These dermal manifestations are usually responsible for an intense and distressing pruritus ani. Allergy and eczema are etiologic factors.

Place the fingertips of each hand on opposite sides at anal verge and use slight traction. *Fissure in ano* will be found at anal verge posteriorly and anteriorly. *Ulceration* near anal

verge, irregular in contour, with jagged edges, grayish base and definite undermining of its periphery, is usually due to a *tuberculous infection*. An ulcer at anal edge, painless, with slightly elevated indurated edge may be due to *chancre*. These usually occur in posterior or lateral quadrants. Rub ulcer base, extract serum and examine for spirochetes. A pustular vesicle or ulcer in the same location with slightly elevated edges, soft and jagged, the floor a dirty yellow color and exuding a foul-smelling discharge warrants examination for the Ducrey streptobacillus. If it is present the diagnosis is *chancroid*. A small ulcer at anal verge with even edges, reddish base, and nonpurulent secretion, especially if present in a Negro, suggests the initial lesion of *lymphopathia venerea*. Do *repeated* Frei tests. An excavated ulcer with coarse fungating granulations along its edge and with firm induration is probably due to *epithelioma*, particularly if the inguinal glands are enlarged. All indurated ulcerations should have tissue removed for microscopic study and interpretation.

A fusiform swelling, bluish in color with its long axis directed inward is usually due to *external thrombotic pile*. The process is caused by the rupture of one or more branches of the interior hemorrhoidal veins and bleeding under the skin. The lesion may be multiple and even involve the entire circumference of the anal outlet and be accompanied by considerable perianal edema. *Never attempt to push this mass into the anal canal!* It belongs outside.

Condylomata are wartlike excrescences, firm to the touch. They arise from the skin edge by a distinctly defined base, are whitish in color, numerous, and are distributed around the margin of the anus, and may even involve the anal canal. They frequently coalesce and form a substantial mass varying in height and surrounding the anal introitus, but the individual stalks are easily differentiated. Luetic growths are not as numerous and are flatter. These warts secrete a very foul-smelling discharge. A Wassermann test should be done in all suspected cases, particularly if adenopathy is present in the groin.

The fingers at the anal verge now exert firmer traction, and

Fig. 139.—Rectocolonic pathology. (Gant.)

the patient is asked to bear down. The lower part of the anal canal is now exposed for inspection. Fissures are more visible. *Internal hemorrhoids*, if present, will be found in the left lateral, right anterior, and right posterior quadrants; *hypertrophied papillae* are seen as dentate projections with whitish tips. *Prolapse of the mucous membranes* is red in color and reducible. If large and protruding from anus several inches and thrown into concentric folds it is due to procidentia recti (all coats of the bowel involved). It should be noted that internal hemorrhoids are entirely covered with mucosa unless they are the prolapsing variety and coalesce with a dilated inferior hemorrhoidal plexus forming the so-called "mixed pile."

Discharges are frequently noted exuding from canal. Their cause must be investigated. Motile *pinworms* are observed occasionally. *Polyps* will prolapse and show outside the canal. I recently saw a three-and-one-half-year-old child with a history suggestive of polyp. Both the mother and the doctor had seen the mass, about the size of a small walnut, protruding from anus. Digital examination was negative. Sigmoidoscopy revealed the tumor 9 inches from the anal verge and filling the lumen of the bowel. I emphasize this case because it demonstrates the degree of prolapse possible. In children, where there is a history of bleeding from the rectum, and palpation and sigmoidoscopy are negative, examination of the large bowel by the double contrast enema method will occasionally disclose a polyp above the realm of visualization. The routine barium enema type of examination is not dependable in this condition.

PALPATION AND DIGITAL EXAMINATION

The perianal region should be palpated for indurations, swellings, fluctuation and crepitation. Any nodular areas should be felt and their consistency noted. Fistulous tracts are palpated as fibrous cords running from the external opening towards the internal opening.

Digital Examination

It is indeed fortunate that at least 90 per cent of the lesions of the rectum are within reach of the examining finger.

Eighty-five per cent of all bowel malignancies and 80 per cent of the strictures are also within this range.

The well lubricated cotted or gloved index finger is gently pressed against the external sphincter until it relaxes somewhat and permits entry of the digit. *Spasm* is due to pathologic tissue within its grasp, such as fissure in ano, thrombotic piles, blind internal fistula with abscess, cryptitis. *Relaxed muscle* is caused by central nervous system lues, chronic prolapse of hemorrhoids or procidentia, trauma to musculature by faulty rectal operations, stricture in lower rectum, fecal impaction and pederasty.

At the mucocutaneous juncture *hypertrophied papillae* are palpable. These may become considerably enlarged, elongated and may assume a polypoid contour. The point of origin differentiates them from adenoma. *Internal hemorrhoids are not palpable*, unless they are fibrotic or thrombosed. The levator ani muscle may be spastic and this phenomenon will be noted as the finger reaches the upper part of the anal canal. *Infected crypts* can be outlined as sensitive, indurated tracts beginning at the meeting point of skin and mucous membrane. *Internal fistulous openings* are palpated as depressions slightly irregular in contour with thickened edge, due to chronic inflammation.

The advancing finger after traversing the anal canal enters the rectal ampulla. Note whether the mucous membrane is smooth or granular, whether or not relaxed. Is bowel wall elastic or is there mucosal thickening or intramural fibrosis? If a *tumor* is palpable, estimate location, size, shape, contour, consistency, whether movable or fixed, how much bowel lumen is involved, whether it is interstitial or extrarectal, pedunculated or sessile. If an intraluminary growth is present it is important to estimate how deeply it infiltrates the bowel wall. Neoplasms penetrating beyond the muscularis have involved the rectal lymph glands. An enlarged, boggy, lacerated uterine cervix impinging on the anterior rectal wall, or fecal masses behind a rectal valve are frequently misinterpreted as malignant growths because of their irregular nodular contour. The mere fact that normal mucosa covers these areas should warrant more thorough investigation.

If the lumen of the bowel is narrowed by *stricture,* is it of a diaphragmatic or fusiform variety? The former is postoperative in origin or caused by cicatrization of chronic inflammatory processes in the bowel. It is usually shallow. The latter may narrow the lumen to varying degrees. The process is in the bowel wall and may be of cartilaginous consistency. Fusiform strictures are most often due to lymphopathia venerea, tuberculoma, syphiloma, sarcoma and leiomyoma. The Frei test and microscopic studies of biopsied tissue are the means of elucidation. A solitary excavated ulcer with raised indurated edges and base is suspicious evidence of carcinoma. Remove tissue for examination. In pedunculated tumors the shorter and broader the pedicle the greater the liability to malignancy.

Occasionally the examining digit in the upper portion of the rectal ampulla encounters an obliterating, firm, irregular, nodular shelf, sometimes cartilaginous to the touch, extending from the anterior surface across the bowel, the only lumen remaining, a strictured area, hardly admitting the fingertip. This is a *Blumer's shelf* and is due to the deposition and growth of cancer cells in the rectovesical pouch from extrarectal cancer. The primary disease may be as high as the stomach. Blumer's shelf is evidence of inoperable malignancy and produces the so-called "frozen pelvis." A similar process may be caused by chronic inflammation, but the consistency is softer and the contour is more rounded.

PROCTOSIGMOIDOSCOPY

Anoscopy

The anal canal should be examined separately. A fenestrated speculum of the Brinkerhof type is excellent for exposing internal hemorrhoids, papillae, crypts and internal openings of fistulae. The genupectoral position is best suited for inspecting lower ampulla. Get the patient to bear down and note whether bowel wall prolapses. If the prolapse comes from above the peritoneal reflection, ascertain by further study whether it is due to an intussusception of sigmoid into rectum. Procidentia below the peritoneal reflection can be satisfactorily combated by perirectal and submucosal injec-

tions of sclerosing solutions. (The former examination is made with a tubular type of anoscope 3 by ⅞ inches with a slightly beveled edge. Other phenomena visible with this instrument will be discussed under "Sigmoidoscopy.")

Sigmoidoscopy

A useful instrument for sigmoidoscopy must be at least 10 inches long and ¾ inch in diameter, be calibrated in inches or centimeters on the outside, be well blackened on inside, be air-tight for inflation, have a beaded tip and be furnished with proximal lighting ample for visualization. The Cameron type of sigmoidoscope meets all these requirements. A telescopic attachment for magnification plus red and green filters are important adjuvants if one desires to make intimate study of bowel phenomena.

The bowel must be thoroughly cleansed by administering 2 ounces of castor oil the night before and by giving an enema with a pint of warm water after the bowels act.

POSITION FOR EXAMINATION.—The knee-chest inverted and exaggerated lateral prone positions may be used. The inverted position requires an expensive table and taxes patients of a nervous temperament and those suffering from asthenia or high blood pressure. In the latter types and in those bedridden and infirm, the prone position is best. For routine purposes I prefer the genupectoral position.

PASSAGE OF THE INSTRUMENT (Fig. 140).—The well lubricated instrument is held in the right hand with fingers on obturator, the left hand retracting the buttocks. The *first position* is downward and forward, the instrument pointing towards the umbilicus. If a painful lesion exists at the anal outlet an application of 1:1000 nupercaine solution will produce sufficient numbing to permit instrumentation. A ½-inch tube can be passed more readily but the lumen is too small for intimate survey. As a last resort local anesthesia may be induced to completely relax the sphincter. Sustained pressure against the external sphincter causes the muscle to relax and the sigmoidoscope begins its journey of exploration. After it has been advanced 2 inches remove the obturator and adjust lighting. The tube now is pointed upward and backward fol-

lowing the concavity of the sacrum until it reaches the promontory. This is the *second position*. Above this point the anterior aspect of the bowel makes a sharp turn to the right; the instrument passes over the prominence and enters the rectosigmoid and sigmoid flexures. The instrument is again pointing downward and forward as in the first position. This is called the *third position*. It is needless to state that from the
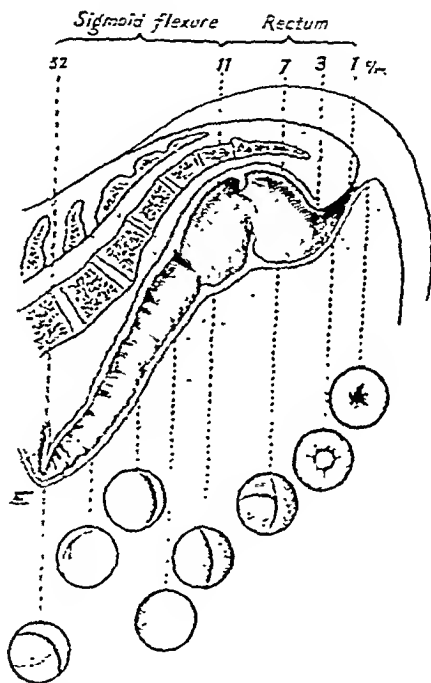
Fig. 140.—Image at different levels. (Bensaude.)

time obturator is removed the tube is passed under the guid ance of the eye going in and during withdrawal, searching behind rectal valves for a possible pedunculated polyp.

Quite often the tube is arrested at the rectosigmoid juncture by spasm of the thickened circular muscle of the bowel (thickened fibers in this region are called "O'Bierne's sphincter"). Sustained pressure for a few moments or the blowing

of a few puffs of air through the inflation attachment will relax muscle, expose lumen and permit further progress. Thickened relaxed mucosa will often require considerable inflation for displacement, so that the lumen of the bowel may be visualized. Where the mesosigmoid is very short, complete passage of the sigmoidoscope is often impossible. *Never use force* in passing any rectal instrument, especially one exploring areas above the peritoneal reflection. The bowel wall may be traumatized and even perforated. Especial care must be exercised in the aged and infirm because of the atonia and inelasticity of the bowel wall. In chronic ulcerative colitis the bowel wall is thinned depending on the depth of the ulcerative process, hence trauma and perforation are to be avoided. In rectal stricture the area immediately above and below the constriction has a poor blood supply, and is more vulnerable to damage.

Phenomena Observed through the Sigmoidoscope.—*Elasticity of the bowel wall* may be estimated by pressure with the end of the examining tube, if it has not been noted during digital examination. Intramural fibrosis from chronic ulcerative colitis, other chronic inflammations and malignancies produce their characteristic changes.

Mucosa is normally pink or salmon colored, has a luster and is smooth. It may be mahogany or brown-black in hue. This is usually due to melanosis coli, produced by taking physics of the anthracene group over a period of time. Withdrawal of the offending drug effects a cure. The blood vessels in the mucosa and submucosa are normally elastic. Pressure with the instrument or by using interrupted suction will permit visualization of the manner of emptying and filling of these vascular arborizations. The contour of the normal vessels is soft and sinuous, but in arteriosclerotic individuals they may be jerky and corkscrew-like, simulating changes in the retinal vessels. The vessels may be injected so that the smaller ones form a fine network imparting to the mucosa a pinkish or slightly reddened appearance. This congestion is frequently the forerunner of more serious trouble but may often be seen after a brisk cathartic has acted.

Lymphoid tissue of the bowel is usually invisible but may

be hyperplastic, discrete or conglomerate and with punc
necrosis. It may appear as hundreds of white specks on
bowel wall, each one about the size of a couple of grain;
sand and evenly distributed as far as the tube will reach, w
healthy mucosa between; or be conglomerate forming sligh
elevated flat plaques of varying size. Where lymphoid hyp
plasia is present, rule out Hodgkin's disease and status ly
phaticus. Visualization of the lymph follicles when enlar;
is enhanced by using the telescopic magnification and a gr
filter.

According to Felsen,[1] "The intestine itself has a *dual exc
tory mechanism*. The first is the *direct excretory route*
substances which have been ingested. These are essentia
products of digestion. The second is the *indirect or hen
togenous excretory route* whereby substances in the blo
stream are brought to the bowel and are excreted though the
vessel wall and mucosa into the lumen of the intestine and so
out of the body." This mechanism explains intestinal mani-
festations of systemic disease. The bowel presents phenomena
that can be interpreted through the sigmoidoscope in such
conditions as plumbism, Hodgkin's disease, status lymphat-
icus, arteriosclerosis, periarteritis nodosa and subacute bac-
terial endocarditis. Telescopic attachment and color filters
must be used for proper interpretation. Time will not permit
a description of these phenomena.

An outstanding example of lesions produced by direct
action is seen in *amebiasis*. In this disease the cysts which have
survived the action of the gastric juice develop into tropho-
zoites and burrow a path underneath the mucosa, elaborating
a histolytic ferment. The tubercle bacillus appears to be
capable of passing from the lumen through intact intestinal
wall. The bowel is the seat of one of the richest lymphoid de-
posits in the body and possesses a vast reticuloendothelial net-
work. The active response of the solitary acuminate lymph
nodules of the intestines is seen in many infections originat-
ing elsewhere in the body. Thus in the case of pneumococcus
Type VII pneumonia in an otherwise normal adult there de-
veloped a diffuse lymphoid hyperplasia throughout the entire
bowel comparable to that seen in status lymphaticus.

Diffuse lymphoid hyperplasia may occur in any infection. In most instances nothing more occurs, the hyperplasia receding with subsidence of the infection. In *acute bacillary dysentery*, however, there is a characteristic three-stage response, viz.: focal lymphoid hyperplasia, succeeded by focal lymphoid necrosis, discrete and confluent ulceration. Even here some mild cases never go beyond the first stage. The three stages develop in twenty-four, forty-eight and seventy-two hours respectively. *Chronic bacillary dysentery* is a perpetuation of stage 3—with geographic, linear or serpiginous areas of ulceration. The distal ileum, proximal and distal colon are the sights of predilection for the intestinal manifestations of most systemic diseases. The essential pathology of chronic dysentery is a cicatrizing, stenosing lesion with mural thickening often accompanied by the formation of inframural abscesses or fistulous tracts.

Polyposis cystica intestini is a form of chronic ulcerative colitis in which the islands of intact mucosa lying between serpiginous, linear and geographic areas of ulceration form pseudopolyps. These polyps do not become malignant and bear no relationship to adenomatosis coli. Many proctologists do not recognize the true nature of these pseudopolyps, advising patients to have them removed to avoid malignancy. I have seen patients with this condition subjected to deep x-ray and even radium therapy.

Ulceration may be superficial and punctate or deep, geographic and serpiginous, and in some instances even exposing the muscularis. The picture in *chronic ulcerative colitis* is essentially that of chronic bacillary dysentery. The bowel may be involved so severely that slightest contact produces bleeding of considerable degree. When the bowel wall gushes pus, it is because of intramural abscesses. The mucosa may be atrophic, dry, with loss of luster and with small plaques of dry stool adhering to its wall. In hypertrophic changes the bowel lining is thickened and thrown into concentric folds which impinge into and frequently hamper the passage of the sigmoidoscope.

Tuberculosis causes a girdling type of ulcer which traverses the bowel, sometimes involving as much as half its breadth.

These ulcers have an irregular edge definitely undermined, and there is a grayish base. Occasionally some dirty yellowish tuberculous nodules are visible in the base.

Amebic ulcers are round or stellate. The mucosa is congested and red. The necrosed base is oval or irregular and appears to project over the level of normal mucosa. There are usually seen yellowish necrotic spots in the ulcers, of the size and color of sulfur granules.

Luetic ulcers are usually broken-down gummata, are apt to be multiple and are often accompanied by stricture. The disease causes plastic deposits in bowel wall causing thickness with lessening of the lumen. The wall is firm and inelastic. The Frei test should be done to rule out lymphopathia venerea.

Ulceration may occur in the rectum and sigmoid from *allergy* and *vitamin deficiencies*, especially of the B group. Felsen states that, "In the allergic intestinal manifestations, sigmoidoscopy may reveal a reddened, edematous, weeping or mucoid mucosa with suggestive wheal-like formation surrounded by a deeply hyperemic halo. This phenomenon may be accompanied by indefinite cramps and bowel irritability and disappears completely with removal of the offending substance or after the use of adrenalin subcutaneously."

Tumors of the Rectum.—Since at least 85 per cent of the tumors of the bowel are within reach of the examining finger such considerations as location, size, shape, consistency, fixity and depth of invasion are best interpreted by the sense of touch. Neoplasms are either intraluminary (impinging into the lumen), interstitial, involving the bowel wall, or extrarectal, penetrating all the bowel tunics and involving other organs by contiguity. The term "extrarectal" is also applied to masses arising in organs outside the rectum, but by pressure narrowing the lumen. If low enough they are palpable. Sometimes these neoplasms will involve the rectum by contiguity. They may even cause perforation in the bowel. This is true of malignant disease in the prostate, uterus and adnexa.

Benign Tumors.—The most frequently encountered tumor in the rectum and sigmoid is the simple *adenoma* or *polyp*. This lesion is usually solitary but may be multiple. It may

be pedunculated or sessile, the pedicle varying from the thickness of a few threads to several inches, the latter in multilobular adenoma. As a rule the shorter and broader the pedicle the more suspicious is the tumor as to malignancy. The polyp itself may vary in size from a small pimple on the mucosa to the large multilobular affair the size of a fist.

Polyps are round or oval in contour but the periphery may be somewhat irregular. The surface is usually granular but may be uneven and ulcerated, depending on trauma inflicted by contracting bowel wall and abrasive action of the passage of hard scybalous fecal masses. It is usually red in color, but gets paler as the pedicle increases in length due to poorer circulation.

It is impossible to state from the physical aspects of a polyp, particularly when the surface is not smooth, as to whether or not *malignant change* has taken place. No polyp should be destroyed by fulguration, unless a suitable portion of it has been reserved for microscopic study.

If polyps are multiple, reddish-purple in color, soft and shiny, some sessile and some pedunculated, suspect *adenomatosis coli*, an hereditary disease. The process may be limited to the rectum but may involve the entire colon and small intestine. X-ray studies by opaque and double contrast enema methods are mandatory. If diagnosis is established, prompt and radical surgery is necessary. On pathologic examination one or several of these tumors will be found with malignant changes.

Other benign tumors found in the terminal bowel are fibroma, lipoma, lymphadenoma, endometriosis, hemangioma, lymphangioma, dermoid cysts and villous tumors (papilloma). Space will not permit a differentiation of these tumors. Their nature will be disclosed by microscopic study.

Malignant Tumors.—The physical characteristics of a palpable tumor are best ascertained by the sense of touch, supplemented by visualization. Malignant neoplasms vary from the excavated indurated ulcer to the rapidly proliferating masses that almost occlude the bowel lumen. Ewing[2] has given us a useful clinical and pathologic classification of these tumors.

If during sigmoidoscopy one notes a foul, putrid-smelling mucosanguineous discharge be suspicious of a malignant process in the vicinity.

The important factors to consider are location of the tumor, its movability, the extent of involvement of the bowel wall and the spread of the growth to other organs. The treatment instituted will be governed by these findings. Microscopic studies of tissue will ascertain the nature of the tumor, degree of malignancy and radiosensitivity.

Sarcoma.—Sarcoma is rare and varies in type as to tissue from which it originates. It is a hard growth, attacking the bowel wall, thickening it considerably and causing stenosis of a fusiform variety. Microscopic study will differentiate the tumor from lymphopathia venerea, hyperplastic tuberculosis and luetic stricture. The Frei test is important.

In profound and unexplained *anemia,* studies of the colon should be made because infrequently a silent tumor in the right half of a large bowel will be disclosed by x-ray.

BIOPSY

Tissue from *every tumor* found during examination should be submitted to the pathologist for diagnosis and grading as to degree of malignancy and radiosensitivity. Biopsy is best performed with a cutting current, utilizing a loop for the purpose. A low voltage current is best, because with it there is a negligible amount of dehydration and hence the bowel wall cannot be involved sufficiently to cause perforation. One must exercise especial care when working above the peritoneal reflection. Tissue for examination may be removed with a biopsy punch, but I have seen alarming hemorrhage after the use of this instrument, and hence prefer the cutting loop or snare.

X-RAY EXAMINATION

Sigmoidoscopic examination should be made prior to any x-ray studies, because tumors in the ampulla, and ulceration frequently are not detectable by the barium enema method of x-ray examination. Every patient with rectal bleeding should have a routine examination of the colon. If sigmoidos-

copy reveals a tumor, x-ray studies are important to rule out a multiple lesion.

In chronic ulcerative colitis, adenoma. multiple polyposis. diverticulitis and diverticulosis, examination must be made by opaque and double contrast enema methods.

For lesions in the cecum and ileocecal region a complete gastro-intestinal x-ray series should be performed. When adhesions are present, the abdominal wall should be pressed on. over suspicious areas. while barium is entering the bowel. particularly if the passage is arrested, these phenomena being observed during fluoroscopy. In suspected sigmoid tumors. roentgen studies in the oblique position will frequently disclose definite information not obtainable with a flat plate.

LABORATORY METHODS

"*Crypt aspirations* are more reliable in isolating B. dysenteriae or endameba histolytica than fecal specimens. particularly in chronic cases. It appears that the bacteria as well as the protozoa tend to lodge deep in the crypts, or. in the case of the endameba. in the submucosal lymphatics. By applying suction to a small localized area of the intact mucosa or to the floor of an ulcer the bacilli or amebae may be often dislodged." (Felsen.[1]) Dr. Felsen has designed a capillary glass aspirator for the purpose. "In amebiasis the fresh material is generally all that is necessary. heating the slide slightly or using a warm stage. Fixation in Schaudinn's fluid followed by iron and hematoxylin staining may be used for supplementary studies. For B. dysenteriae the withdrawn material is sprayed on an Endo plate or other culture media necessary for the growth of the organism."

The *Wassermann test* should be done in all rectal strictures. inguinal adenopathies, suspicious ulcers or warts in perianal region. The *Frei test* should be carried out in all rectal strictures, enlarged abscessed inguinal glands. suspicious ulcers at anal verge or fibrous conditions in anal canal or rectum. to rule out the possibility of lymphopathia venerea.

In pruritus ani *skin scrapings* should be examined for fungi and be cultured. In women, *vaginal smears* should be scrutinized for Trichomonas vaginalis as a possible etiologic fac-

tor in pruritus. Routine *urine analysis* will rule out diabetes.

A complete *blood count* is necessary before any rectal operation or where the lesion in bowel may have produced an altered blood picture. For ova of intestinal parasites, a small portion of *stool* removed through a sigmoidoscope is adequate for examination.

Agglutination tests for B. dysenteriae should be performed.

Microscopic study of every tumor or suspicious tissue is obligatory. In tuberculous ulcers biopsy material should be examined and the discharge, if otherwise negative, should be injected in a guinea pig.

SUMMARY AND CONCLUSIONS

1. Every case of bleeding from the rectum should be considered potentially malignant unless proved otherwise.

2. Every patient with a rectal complaint should be given the benefit of indicated methods of examination.

3. Every tumor or induration should be biopsied and tissue submitted for microscopic study.

4. X-ray surveys should *follow* sigmoidoscopy.

5. Discharges from ulcers and suppurations should be submitted for bacteriologic investigation. Frei and Wassermann tests should be performed when deemed necessary.

6. Periodic health examinations should include routine sigmoidoscopy and examination of the colon when symptoms warrant.

7. Medical colleges and hospitals must be staffed with men competent to teach diagnostic methods and interpretation of disease in the rectum and colon.

BIBLIOGRAPHY

1. Felsen, J.: Intestinal Manifestations of Systemic Disease. Rev. Gastroenterol., 5 (2): 114–132 (June) 1938.
2. Ewing, J.: Neoplastic Diseases, 4th Edition. W. B. Saunders Co., Philadelphia, 1940, pp. 686–703.

THE ACUTE ABDOMEN

GUILFORD S. DUDLEY, M.D.*

THE purpose of this discussion is to bring to your attention the outstanding signs and symptoms of the acute abdomen. No detailed diagnostic review is intended since such is readily available in any standard textbook.

ACUTE APPENDICITIS

The most common cause of the acute surgical abdomen is inflammation of the appendix. Failure to recognize this lesion in its early stage probably accounts for the fact that its mortality rate is approximately the same today as it was ten or twenty years ago.

Acute appendicitis is usually of abrupt onset. The patient is frequently awakened from sleep with cramplike upper or midabdominal pain associated with nausea or vomiting. In from four to six hours after the initial symptom the pain becomes of a constant nature and localized to the right lower quadrant. Operation performed at this early time often reveals extensive inflammatory involvement of the appendix. *The longer operation is postponed the more grave may be the degree of inflammation.* The rapidity with which inflammatory changes take place varies widely. While it is well recognized that in some instances the inflammation may subside spontaneously, it is equally as well recognized that no one of us can predict which particular case will subside, will perforate, will localize the intraperitoneal infection, or will develop diffuse spreading peritonitis. For this very simple reason, *it must be urged strongly that every case diagnosed as acute appendicitis be submitted to operation at the earliest possible time.*

Acute appendicitis progresses with extreme rapidity in the young and in the elderly. Beware also of acute appendicitis

---

* Director, Second Surgical Division, Bellevue Hospital.

in the *obese* patient. Here the symptoms and signs are prone to be minimal and localization of the infection ineffectual.

DIAGNOSIS.—The one single and *most important physical finding* in acute appendicitis *is localized tenderness to pressure*. This localized tenderness is usually at the level of Mc-Burney's point in the right lower quadrant. By the term "tenderness to pressure" emphasis must be made that this be *gentle* pressure. Firm, rough, forceful pressure will elicit tenderness in almost any abdominal examination. Such type of pressure should not be used.

The *second most important physical finding is rebound tenderness*. Muscular rigidity may or may not be present and its absence should not rule out the existence of acute appendicitis. The well-worn adage that the difference between a surgical specialist and the general practitioner in making a diagnosis of acute appendicitis is that the specialist is one who performs a digital rectal examination deserves to be discarded. Digital rectal examination not performed gently will almost always cause pain. Seldom does it give valuable information not obtainable from careful abdominal examination.

The average patient with acute appendicitis has a moderate fever, usually less than 101° F., and a leukocytosis in the neighborhood of 15,000. A fever above 101° F. and a leukocytosis above 20,000 is unusual. It must be borne in mind, however, that acute appendicitis may be present in the absence of fever, in the absence of leukocytosis, in the absence of nausea or vomiting, and that it may manifest only localized tenderness to gentle pressure in the right lower abdomen. *Persistent preoperative vomiting* is an ill omen; it usually signifies extension of the inflammation and a spreading peritonitis.

TREATMENT.—Once the diagnosis or the presumptive diagnosis of acute appendicitis is made there is but one treatment, namely, operation. *The use of any cathartic is distinctly contraindicated* because of the danger of the spread of infection within the peritoneal cavity as the result of active peristalsis. *Sedation by the use of morphine* should be employed only with the full knowledge that operation is to be carried out immediately. The use of an ice bag or of a hot water bottle

locally does not influence the progress of the inflammation one way or the other. The counterirritant action of the heat or of the cold does give relief to the pain but it also masks the severity of the local tenderness and may mislead one from accurate diagnosis.

As has been stated before, the failure to reduce the mortality rate in acute appendicitis over the past two decades is due to the failure to submit every case to operation at the earliest possible time. It is far more justifiable for the conscientious physician or surgeon to remove an occasional normal appendix as the result of a mistaken diagnosis than it is to permit a single patient with appendicitis to have his operation postponed with resultant fatality.

By choice, every operation for acute appendicitis should be accompanied by the removal of the appendix. However, in the occasional difficult or delayed case it is fully justifiable and advisable to institute only drainage of the peritoneal cavity. After recovery such case should be submitted to an operation of election through an adequate exploratory incision for the removal of the appendix.

TERMINAL ILEITIS

Within the past few years recognition has been made of an inflammatory process involving the terminal ileum and at times extending to involve the cecum. At first this process was believed to be confined to the terminal ileum and cecum for which reason the name "terminal ileitis" was applied. Further observation has brought to light the fact that such inflammation may also involve other segments of the small intestine and the term "segmental enteritis" (Lewisohn) was introduced to cover this fact.

The symptoms of terminal ileitis or segmental enteritis may lead one into a mistaken diagnosis of appendicitis. The symptoms usually are more indefinite than in acute appendicitis and as a rule one would not expect the local tenderness of the latter. The inflammation of the small intestine presents a more long-standing picture of diffuse, cramplike abdominal pain associated with a constant low grade fever and usually diarrhea.

PERFORATED PEPTIC ULCER

This is the second most commonly encountered acute surgical lesion of the abdomen. In a series of 104 cases at Lenox Hill Hospital reported by Meyer[1] there were eighty-one perforations of gastric ulcer and twenty-three of duodenal ulcer. Seventy-six of the eighty-one patients with gastric ulcer perforation and twenty-two of the twenty-three with duodenal perforation were male. Perforation of either gastric or duodenal ulcer rarely occurred in the very young or the very old. The average age was the early part of the fifth decade.

DIAGNOSIS.—Perforated peptic ulcer is the one condition associated with *true, unmistakable boardlike muscular rigidity*. The accompanying pain is exquisite and is confined to the upper abdomen, usually the epigastrium. Nausea and vomiting may occur but frequently do not. The *absence of liver dulness* is an important sign: this absence indicates a condition of pneumoperitoneum or air between the liver and the diaphragm, and is indicative of perforation of a hollow organ, usually the stomach or duodenum, more rarely the small intestine. Failure to demonstrate gas by roentgenologic examination may occur in more than 25 per cent of cases of perforation of the stomach or duodenum. The leukocyte count is high. In Meyer's series it averaged 14,900 in the gastric ulcer cases and 13,300 in the patients with duodenal ulcer. There was an average of 85 and 84 per cent polymorphonuclear leukocytes, respectively. In many instances the counts were much higher, but in the very critical cases the polymorphonuclear leukocytes were low, indicating poor resistance. In every such instance the patient died.

Careful questioning may or may not reveal a previous history suggestive of ulcer. It is often found that such ulcer symptoms have been of an aggravated nature during the week preceding actual perforation, and it is not uncommon for the actual perforation to be associated in the patient's mind with some unusual physical activity. The mortality rate tends to be slightly higher in gastric ulcer perforations with no previous ulcer history. History of previous ulcer symptoms is the rule in duodenal ulcer perforation. In 21 per cent of Meyer's cases of perforated gastric ulcers and in 8.6 per cent

of his cases of perforated duodenal ulcers, the rupture occurred without a previous history.

TREATMENT.—There is an old saying, "The sun must never rise or set in perforations of the gastro-intestinal tract without an attempt at relief."

This is as true today as when first uttered. Perforations of the gastro-intestinal tract are always serious as to prognosis. As Meyer points out, "They must be considered either as an emergency or an urgency. The higher (esophagus) or lower (colon) in the gastro-intestinal tract the perforation occurs, the more serious the outlook. Mortality is very high and the chance of the patient's recovery is problematic unless an early diagnosis is made."

Mortality is in direct ratio to the lapsed time between perforation and operation. Eliason and Ebling[2] state that if operation is performed within six hours, the mortality is 7.5 per cent; from six to twelve hours, 32.9 per cent; from twelve to twenty-four hours, 35.4 per cent, and from twenty-four to forty-eight hours, 67.5 per cent. Meyer found that the average lapse of time in the successful cases was 4.4 hours in the gastric ulcer group and 12.8 hours in the duodenal cases; the average time in the fatal cases was 24.4 hours in the gastric and 29.6 hours in the duodenal ulcer group.

Acute perforation of a peptic ulcer in the first few hours causes a chemical peritonitis which soon becomes bacterial. At operation no procedure should be carried out other than simple closure of the perforation. As a working basis, it is generally assumed that, after ten hours have elapsed from the time of presumptive diagnosis of perforation, a bacterial peritonitis has ensued. For this reason it is common practice to close the abdomen without drainage if operation is performed before ten hours, and to institute peritoneal cavity drainage if operation is performed after ten hours have elapsed. It is recognized, also, that an acutely perforated peptic ulcer may spontaneously close its perforation by becoming adherent to the undersurface of the liver, but the recognition of this fact does not in any way justify postponement of operation. Subsequent treatment of the perforated peptic ulcer should be guided by the patient's clinical course.

If symptoms can be controlled by diet and a medical regimen the question of secondary operation may be postponed. Second and even third perforations of a peptic ulcer may take place. With this knowledge at hand the individual patient may elect to take his chances on re-perforation rather than his chances on an extensive resection of the stomach.

ACUTE INFLAMMATION OF THE GALLBLADDER

Another lesion with which the practicing physician is often confronted is acute inflammation of the gallbladder. For many years it was rather customary not to consider this infection as an urgent surgical problem. Opinion today is changing. The frequently reported instances of rupture of suppurative cholecystitis with associated upper abdominal peritonitis and death emphasize the surgical urgency of this lesion. It is now accepted that clinical and laboratory findings are not necessarily closely associated with the pathologic progress of the inflammation of the gallbladder. To put it another way, one cannot always judge by physical examination the severity of the inflammation. One cannot determine before operation which inflamed gallbladder will perforate and which will subside. Furthermore, *it is less dangerous to the patient to remove the acutely inflamed gallbladder than it is to remove the chronically inflamed gallbladder which has been involved by previous acute infections*. The mortality rate is distinctly more favorable as a result of early than of postponed operation. By early operation is meant one performed within forty-eight hours of the onset of symptoms; moderately early operation—one performed within five days of operation; and late operation—one performed after the clinical signs and symptoms have subsided. Graham[3] has reported a series of 167 cases of acute cholecystitis; *in those cases operated upon within forty-eight hours of the onset of the attack there was a mortality of only 3.59 per cent; in those operated on within five days the mortality was 5.13 per cent; after that period it rose to over 20 per cent. There are many other reports in the literature showing similar results.*

Symptoms.—The acutely inflamed gallbladder presents with severe right upper abdominal pain associated with fre-

quent vomiting and often a palpable mass immediately below the free margin of the liver. There is also well localized tenderness and perhaps moderate muscular spasm. Frequently the pain radiates toward the back and upward to the region of the right shoulder, posteriorly. A temperature of 102° to 104° F. is not uncommon. This grade of fever is greater than is noted with acute appendicitis. Jaundice is not present as a rule, and the pain tends to be of a more constant nature than the colic-like pain associated with cholelithiasis.

Treatment.—The surgical procedure of choice is removal of the acutely inflamed gallbladder and drainage of the gallbladder bed in the liver to the level of the ligated cystic duct. We all appreciate the value of cholecystostomy with drainage of the gallbladder itself as a life-saving procedure in the exceedingly ill patient. Cholecystostomy with drainage, however, is not a curative act and, therefore, should almost always be supplemented by elective cholecystectomy at a later date.

Incidence.—Acute inflammation of the gallbladder while it occurs in the male is much more frequent in the female, particularly in the woman in her fourth or fifth decade. Previous pregnancies and typhoid fever are felt to be predisposing factors in the incidence of the lesion.

ACUTE INTESTINAL OBSTRUCTION

Acute intestinal obstruction may be of a mechanical nature and with or without strangulation, or it may be of the nature of a paralytic ileus.

Mechanical Intestinal Obstruction

Mechanical intestinal obstruction has many causes. The small intestine becomes mechanically obstructed by intraabdominal bands or adhesions, by strangulated herniae, either external or internal, by a gallstone, by intussusception in children, or more rarely by volvulus or a neoplasm. The large intestine becomes mechanically obstructed usually by a neoplasm of the left half of the colon, by volvulus of the sigmoid or cecum, or by fecal impaction. *Persistent vomiting without an adequate explanation of its cause is an excellent indication for exploratory laparotomy.* An x-ray film of the abdomen

often is of value in giving one a clue to the location of the obstruction.

Acute mechanical obstruction of the large intestine by neoplasm must be relieved by colostomy proximal to the neoplasm. Surgical attack upon the neoplasm itself should never be attempted in the presence of acute obstruction but is to be carried out at a later date and in accordance with the findings of the individual case.

Obstruction of the small intestine must be overcome by the release of the band of adhesions, by the release of the strangulated hernia, by the removal of the obstructing gallstone or tumor, or by the untwisting of the volvulus. Never attempt to reduce a hernia of any type in which there is any question of strangulation. It may be reduced "en masse" and the strangulated intestine remain strangulated. Never omit palpation of the region of the femoral canals in order to rule out strangulated femoral hernia. If the strangulated small intestine is no longer viable, immediate intestinal resection and restoration of the continuity of the lumen of the small intestine must be carried out.

Acute mechanical obstruction due to volvulus of the cecum or of the sigmoid is to be relieved by reduction of the volvulus, and the fixation of the bowel to obviate recurrence of the volvulus.

In *acute mechanical obstruction due to intussusception* the intussusception is to be reduced if possible, and appropriate measures should be taken to obviate a recurrence.

CORRECTION OF DEHYDRATION.—While it is imperative that these measures for the relief of acute mechanical intestinal obstruction should be undertaken without delay, nevertheless it is equally urgent that the patient's dehydration from loss of fluids also be combated. This can be rapidly done during the stage of preoperative preparation by the intravenous administration of 5 per cent glucose in normal saline solution and can be similarly continued into the postoperative period.

DECOMPRESSION OF THE INTESTINE.—The rather recent introduction of a *double lumen rubber tube* (Miller-Abbott tube) for decompression of the distended intestine is an added feature in the management of acute obstruction. This

tube, passed through the nose into the stomach, is carried by peristalsis through the pylorus into the duodenum. When it has entered the duodenum, a small balloon attached to one of its lumina is inflated. This inflated balloon acts as a bolus. The content of the small intestine is aspirated through the second lumen constantly and the tube moves forward through the small intestine by peristalsis. In this manner, general abdominal distention may be greatly relieved and operative intervention markedly facilitated. It is even advocated in selected instances that a small quantity of a dilute solution of barium may be introduced into the intestine through this tube and the site of obstruction identified by x-ray. This double-lumen tube, however, is a two-edged sword. If not utilized with discretion it may be a factor in delay of operation of exceedingly serious import to the patient. Employed as a decompressing agent in paralytic ileus, in which lesion there is no one single mechanical obstructing favor, this double-lumen tube is invaluable.

Paralytic Ileus

Paralytic ileus is usually a postoperative complication dependent upon diffuse infection within the peritoneal cavity. Obstruction in this instance is due to the sum total of the paralyzing effect of peritonitis on the musculature of the bowel wall plus a multiplicity of kinks and angulations of the bowel by fibrinous exudate but without any single site of complete occlusion of the bowel lumen. Paralytic ileus is the type of intestinal obstruction which, with subsidence of the peritonitis and restoration of muscular activity in the bowel wall, tends to go on to recovery without the mechanical relief of any single obstructing factor. This type of intestinal obstruction is particularly amenable to the use of the double-lumen (Miller-Abbott) tube, stimulating drugs (prostigmine or eserine), colonic irrigations, and gastric lavage.

MESENTERIC THROMBOSIS

Mesenteric thrombosis associated with gangrene of a segment of the small intestine gives an almost 100 per cent mortality rate. Following resection of the gangrenous intes-

tine, the thrombotic process tends to extend to the blood supply of the uninvolved intestine. Hope for the reduction of this high mortality rate may arise from the use of recently introduced drugs (*e.g.*, heparin) which have the property of prolonging the normal blood clotting time and thereby of preventing extension of a thrombotic process.

The presenting symptom is *intense midabdominal pain* with cessation of intestinal activity. In effect, it presents as an acute intestinal obstruction, although frequently bloody liquid fecal material may be obtained by enema or colonic irrigation. An associated cardiac valvular lesion may give one a clue to the diagnosis of this condition.

ACUTE HEMORRHAGE INTO THE PERITONEAL CAVITY

Acute hemorrhage into the peritoneal cavity may arise as the result of a ruptured, extra-uterine pregnancy, and occasionally as the result of the rupture of a graafian follicle.

The outstanding feature of hemorrhage from a *ruptured, extra-uterine pregnancy* is fainting, or swooning. Associated with this is occasionally the history of an irregularity in menstruation, with intermenstrual bleeding, pain in the right or left lower abdomen, and a positive Aschheim-Zondek test.

When the *rupture of a graafian follicle* is complicated by profuse bleeding, the picture is similar to that of hemorrhage due to a ruptured, extra-uterine pregnancy, except that there is no history of menstrual irregularity and no positive Aschheim-Zondek test.

Acute intraperitoneal hemorrhage is accompanied by leukocytosis but not by fever. Pelvic examination reveals marked tenderness on movement of the cervix and often a mass in one side of the pelvis.

ACUTE SALPINGITIS

Acute salpingitis presents no history of fainting and is accompanied by discomfort and pain in both sides of the lower abdomen. Nausea, vomiting, fever and leukocytosis are also present.

When this condition is due to infection by the gonococcus it does not call for operative interference. The reason for this

is not that removal of the acutely inflamed gonorrheal fallopian tube is attended with any high degree of mortality, but because such an acutely inflamed fallopian tube may return spontaneously to normal. Should one open the abdomen under a mistaken diagnosis of acute appendicitis and find a purulent exudate from the fimbriated extremity of a fallopian tube, there is no indication for the removal of this tube.

ACUTE PANCREATITIS

Acute pancreatitis is ushered in by exceedingly severe epigastric pain which tends to radiate directly through to the back at the same level. At the onset, vomiting is usual and the pain tends to remain localized in the epigastrium. The severity of the symptoms varies with the severity of the process and in some instances death occurs within forty hours.

The difficulty in differentiating accurately between acute pancreatitis and other acute lesions that might be amenable to surgical relief is the real reason for operation in this disease. Many question the value of drainage of the pancreas or of the gallbladder in acute pancreatitis and believe that if accurate preoperative diagnosis could be made, acute pancreatitis would not be an indication for operation.

TRAUMA TO THE ABDOMEN

With Perforation of the Abdominal Wall

Stab wounds, gunshot wounds or other wounds involving penetration of the abdominal wall may cause injury to any of the intra-abdominal viscera.[a] All such penetrating wounds should be treated by laparotomy at the earliest practicable time. Severe shock calls for immediate supportive measures such as infusion and transfusion to prepare the patient for laparotomy. *Rents* or *tears* in the large intestine are probably better handled by exteriorization of the injured colon which then may be closed at a later date. In the instance of bullet wounds there is almost always more than one opening through the intestine and it is imperative that *all* openings be closed. Possible break in the retroperitoneal portion of the duodenum must not be overlooked.

Without Perforation of the Abdominal Wall

Trauma may cause a rupture of the small or large intestine by compression of the gut against the vertebral bodies or by a pneumatic blow-out. It is usually the *small intestine* which suffers rupture due to trauma, although occasionally a redundant sigmoid colon may be affected.

Rupture of the urinary bladder may result from trauma. Distention of the bladder by urine at the time of injury predisposes to its rupture. Bladder rupture may be intraperitoneal or extraperitoneal. This injury calls for immediate repair and suprapubic drainage of the bladder.

Rupture of the spleen is amenable to splenectomy. It is not practicable to repair a splenic tear by suture or tamponade because of the danger of subsequent hemorrhage. This is exemplified by those instances of ruptured spleen which through mistaken diagnosis are not operated upon at the time of injury and which apparently recover but must be operated upon seven to ten days following injury because of severe late hemorrhage. *Removal of the normal ruptured spleen is completely compatible with continued good health.*

Rupture of the liver, if small, may be controlled by suture. If large, the rupture is almost uniformly fatal though it can be controlled temporarily by tamponade.

Severe Contusions of the Abdominal Wall

Not infrequently contusions of the abdominal wall are associated with other trauma. Abdominal wall contusion alone, without severe intra-abdominal injury, may present a muscular rigidity indistinguishable from an intraperitoneal injury. Oftentimes careful observation with evaluation of associated injury to the thorax will contraindicate an abdominal operation which, under other circumstances, would appear to be clearly indicated.

Supportive Treatment of Traumatic Conditions

Morphine should be used for the alleviation of pain in any of the foregoing traumatic conditions, but its use must be governed by extreme care so as not to mislead the observer in making a diagnosis. In some of the air raid injuries in Eng-

land, the quantity of morphine given by the doctor administering immediate treatment to the victim is marked on the individual's forehead.

BIBLIOGRAPHY

1. Meyer, Herbert Willy: Perforations of the Gastro-intestinal Tract. Ann. Surg., March and July, 1940.
2. Eliason, E. L. and Ebeling, W. W.: Am. J. Surg., 24: 63–82 (April) 1934.
3. Graham, Henry F.: Surg. Clin. North Amer., 20: 511–521 (April) 1940.
4. Dudley, Guilford S.: Acute Abdominal Injuries. Surg. Clin. North Amer., April, 1935, pp. 345–359.

THE NATURE AND TREATMENT OF CHRONIC CONSTIPATION AND CHRONIC DIARRHEA*

ASHER WINKELSTEIN, M.D.†

CONSTIPATION

DEFINITION.—Various authors define chronic constipation differently. According to Hurst, when a meal is taken eight hours after a defecation and none of the residue of that is excreted within forty hours, the patient is constipated. Faber uses these criteria: if the patient has less than one bowel movement daily; or, if the stool is hard; or, if laxatives are necessary for a bowel movement. If we add the subjective sensation of an incomplete evacuation to Faber's criteria, the definitions given by him and Hurst seem adequate.

If one studies the daily feces of a healthy young adult, one finds, as a rule, one formed stool, occasionally two, of medium consistency, of a medium brown color without much gas or foul odor. A slight amount of mucus may be considered normal.

In this discussion we are not referring to temporary or acute constipation as a result of psychic disturbances or acute illnesses, nor are we referring to constipation caused by inflammation, by internal or external compression, or by diseases outside of the colon.

Causes

1. Lack of exercise with increased psychic activity.
2. The failure to respond to the defecation reflex (the "call of nature").
3. The use of irritant laxatives, following which the bowel is empty so that there is insufficient stimulus; or the stimulus from the laxative has been so great that the subsequent

normal stimulus is too weak to produce a bowel movement.

4. Weak abdominal muscles particularly in women after pregnancy and after abdominal operations.
5. Nervous dysregulation of the colon.
6. Too little or too much roughage in the diet.
7. Misuse of coffee, tea, chocolate and tobacco.
8. Dryness of the stool due to:
    (a) Too little fluid intake.
    (b) Excessive absorption of fluid.
    (c) Increased perspiration.
9. The causes of rectal constipation will be discussed later.

The question of *mechanical causes* arises. Claims have been made that Jackson's bands and Lane's kinks (which may be due to the vertical or upright position of the human animal) play a role, and partial colectomy and division of the bands and adhesions have been advocated in the treatment of chronic constipation. I believe that mechanical factors are not important in chronic constipation.

Enteroptosis has been accused as an etiologic agent. However, radiologic studies reveal a fairly high incidence of ptosis in normal people with normal bowel movements. When the ptosis results from weakened abdominal wall muscles it may play a role. In addition to visceroptosis, other anomalies have been mentioned as causes of chronic constipation. Among these are a *low or high cecum*, *redundancies* at the flexures, particularly the sigmoid, and *elongation of the bowel* especially in the sigmoid region. It seems fair to conclude that these mechanical factors and anomalies may play a subordinate role as predisposing factors in chronic constipation.

The psychic, constitutional, or *nervous system element* seems to be the most important factor in the large percentage of cases of chronic constipation. It is probable that chronic constipation is not a problem of mechanical disturbance but one of disturbed nervous regulation of the motor and secretory activities of the gastro-intestinal tract. In other words, it is largely a functional disturbance. Today, it is generally considered a "psychosomatic disease."

Incidence.—Chronic constipation usually commences early in life and has an equal incidence in the male and female sex.

Classification.—One may classify chronic constipation into two groups, namely "colonic" and "rectal." The rectal group is often called "dyschezia" (Hurst) which means painful defecation.

Colonic Constipation

In this group the stasis is, in 20 per cent of the cases, in the right colon from the cecum down to the first portion of the transverse. The stool may remain there from one to three, or even five days. In a smaller group, perhaps 10 per cent, the stasis is in the transverse colon. In the others, it is in the descending colon and sigmoid.

There has been a great deal of discussion as to whether the constipation in the colon is due to a disturbance of the regulation of the peristalsis that results in stoppage in movement of the stool at certain parts, where it causes secondary irritation and spasm, or whether it is due to a weakness in the muscle itself particularly in older individuals and in postoperative cases, so that actually there is an atony or lack of *vis a tergo* in the colon. Alvarez denies the existence of an atonic type of constipation and claims that he has never seen it radiologically. However, in my personal experience, in older individuals and particularly in women after pregnancy and abdominal operations, where the abdominal wall is lax, one does see a colon which is quite wide and with marked stasis especially in the transverse colon. Nevertheless, most of the chronic types of constipation are spastic.

While the classification of chronic colonic constipation into ascending, transverse and descending types is usually given, in my experience a large number of patients with spastic constipation have merely a slow progress of the stool through the colon. The barium meal may take from two to three days to pass gradually through the colon.

In the colonic type of constipation the mechanism of evacuation from the rectum may be perfectly normal, but there is instead a delay in the arrival of the stool at the rectum itself.

Dyschezia

In the second type of chronic constipation, the movement through the bowel may be normal, but the rectum fails to empty itself. At times there is a daily movement, or more than one daily movement, but the evacuation is fragmentary. This is misleading and often the patient states that he has a regular bowel movement, whereas the examining physician may find a rectum filled with fecal matter shortly after a bowel movement. This incomplete or fragmentary type of constipation is frequently encountered.

The *causes* of rectal constipation or dyschezia are:

1. Laziness or bad habits on the part of the patient which lead to a loss of the reflex.
2. A bad position at defecation—in most people the thighs are insufficiently flexed toward the abdomen at evacuation.
3. The presence of local irritation and inflammation which, according to Alvarez, leads to a reversal in the gradient of the rectum. There is the familiar effect of hemorrhoids, painful fissures, proctitis and cryptitis in producing constipation.
4. There also exists definitely, as a result of psychic disturbance, functional spasm of the internal sphincter. Furthermore, the sphincter may be spastic as a reflex from disease in neighboring organs in the pelvis.

It is obvious that, when the radiologic examination reveals a normal movement through the colon, but a stasis in the rectum, the use of irritating laxatives and purgatives is unnecessary and unwise. Often the mere use of a small amount of water in the rectum as an enema will produce a good bowel movement in such individuals.

It should be stated that rectal constipation forms over half (approximately 60 per cent) of the cases of chronic constipation.

Symptomatology

There may be no symptoms. There are a few patients on record who have a bowel movement but once in several days without any symptoms whatsoever resulting from the reten-

tion of waste. However, in most instances there is at least a psychic reaction to the condition and often definite symptoms arise. The patients may complain of the *general symptoms* of headache, dizziness, foul breath, furred tongue, anorexia, nausea, insomnia and irritability—all part of the concept of "intestinal auto-intoxication," which will be discussed later.

Local symptoms include distention or flatulence, gurgling noises and sticking, colicky or dull pains.

There is, at times, a definite *gastric symptomatology* of chronic constipation, such as epigastric pain, heartburn, belching, vomiting and even the clinical picture of peptic ulcer. These gastric symptoms have been entitled "intestinal dyspepsia." At times they are brought about by some underlying condition such as a psychic disturbance affecting the entire gastro-intestinal tract. At times the gastric symptoms are produced reflexly, or by direct pressure effects. For example, in sigmoid spasm with stasis in the sigmoid, distention of the colon with an accumulation of gas in the splenic flexure often produces pressure in the upper abdomen particularly involving the stomach. Pressure against the greater curvature and posterior wall of the stomach may produce the familiar "cascade stomach" which is often associated with gastric symptoms. A "gurgling" cecum and a tender, cordlike spasm of the sigmoid are common.

Inasmuch as chronic spastic constipation occurs frequently in women with constitutional enteroptosis and marked neurotic tendencies, the clinical pictures of severe anorexia even leading to typical anorexia nervosa and hysterical vomiting followed by emaciation are not rare.

It should be pointed out here that while proctitis, cryptitis, fistula in ano, fissures and hemorrhoids may be the cause of chronic constipation, in many instances they are also the result of constipation, particularly of the rectal type.

Intestinal Auto-intoxication

There is very little evidence of a convincing nature that patients actually suffer from a poisoning from the intestinal tract in chronic constipation. Eskimos who consume an

average of 8 pounds of meat daily almost never reveal evidence of intestinal intoxication. The fermentation of carbohydrates does not lead to poisoning. The putrefaction of proteins in the colon, producing indol, skatol and phenol, does occur and there is a slight absorption of these poisons. However, the amount produced is minute and their detoxification by the liver and excretion in the urine is usually quite complete. *Histamine* has been incriminated. Histamine is produced by the breaking down of histidine by the bacteria in the intestines. However, histamine itself is largely destroyed at once in the colon and if absorbed it is taken care of by the liver. Enormous quantities of histamine, as much as 500–700 mg., have been given by mouth without the production of any systemic effects whatsoever. Some feel that the bacteria in the colon may give off *exotoxins* and, if killed, *endotoxins*, which may play a role, but there is very little evidence to support this view. However, it has been demonstrated that bacteria from the colon may enter the lymphatics and grow in the lymph nodes. Some claim that distant symptoms such as infectious arthritis may be produced in this way.

The entire question of the production of poisonous and toxic substances in the colon and their absorption is today very unclear. It is probable that there is a production of large amounts of toxic substances but that very little is absorbed, and when they are absorbed the detoxifying activity of the liver is sufficient to protect the individual. Theoretically, it is possible, particularly if the liver is mildly and chronically impaired either by these toxins or by a local disease such as gallbladder disease or hepatitis, that the toxins and poisons may gain access to the body and produce remote toxic effects. This subject requires further study.

There is a great deal of evidence that the symptoms of auto-intoxication are due to *mechanical* and *reflex* causes. Alvarez in 1924 wrote on this subject and claimed that because the rectum is very sensitive to rises in pressure (even 2–3 mm. change in pressure produces symptoms and 20–60 mm. rise of pressure may make the patient very uncomfortable), he feels that most of the symptoms ascribed to intoxication are reflexes from mechanical distending effects in the

lower bowel. If normal individuals are asked to refrain from a bowel movement for three or four days, many of these symptoms set in and are strikingly relieved, usually within an hour, by an enema. It is probable that many of the symptoms, such as the coating of the tongue, bad breath and nausea, are due to *antiperistalsis*, and that other symptoms are due to reflexes. It seems unlikely that the relief of symptoms would occur within an hour or two after an enema if they were actually due to an intoxication. As Alvarez put it very wittily, "The removal of a glass of whisky from a drunkard would not relieve the drunkenness at once."

Treatment of Constipation

Patients with chronic constipation should always be examined with the greatest care for the presence of organic disease. Most patients who fail to respond to the usual forms of therapy for chronic constipation have an undiagnosed organic condition.

In treating chronic constipation the complexity of the situation and the importance of a complete cooperation over a long period of time by the patient should be pointed out. The object of the treatment should be for the patient to have a daily spontaneous bowel movement of a normal amount, consistency *and* odor. The patient must be examined thoroughly and in addition to the usual examinations the following should especially be investigated:

1. Gastric acidity and motility.
2. The rate of motility through the colon.
3. The rate of small intestinal motility.
4. The width and haustration of the colon.
5. A careful local examination of the rectum and sigmoid including proctoscopy and sigmoidoscopy.
6. A careful examination of the anal sphincter and canal.
7. The exact dietetic and bowel habits of the patient.
8. An examination of the stools after the patient has been on a mixed diet for a few days. For special purposes the meal may be demarcated by giving charcoal or carmine before and after the given meal.

DIET.—In all cases it is advisable to commence the therapy with a *bland, nonresidue diet,* similar to that used in the ambulatory treatment of peptic ulcer. The writer's diet is given here. After two weeks of this diet, it is possible in most cases to return to a normal mixed diet.

BLAND, LOW RESIDUE DIET FOR CONSTIPATION AND DIARRHEA

GIVE:

Vegetables
Tomato juice, purée or strained vegetables, asparagus, carrots, string beans, spinach, tomatoes, peas, boiled, mashed, or baked potato.

Fruit
Stewed fruit without skin or seeds as pears, peaches, applesauce, ripe bananas, strained orange or grapefruit juice.

Bread and Cereals
Well-cooked cereal or cereal without bran as cornflakes, puffed wheat, etc., white bread.

Dairy Products
Boiled milk, buttermilk.
Eggs, soft or hard boiled or poached.
Cheese—cream, cottage, or pot.

Meats
Tender meat, fish or chicken—not fried.

Miscellaneous
Thin cocoa, weak tea.
Simple desserts—cornstarch pudding, tapioca pudding, custard, plain gelatin, junket, jelly.

AVOID:

Vegetables
Raw vegetables.

Fruit
Raw fruits.

Bread and Cereals
Bran cereals as shredded wheat or krumbles, whole grain breads, whole wheat and pumpernickel.

Meats
Pork and veal.

Miscellaneous
Spices and condiments other than salt.
Coffee and strong tea.

TYPE DIET:

Breakfast
 Orange juice, grapefruit juice, or stewed fruit without skins or seeds.
 Eggs, soft or hard boiled or poached, or well-cooked cereal with
  milk and sugar.
 White bread or toast with butter or jelly.
 Buttermilk, thin cocoa, or tea.

Noon Meal
 Tomato juice.
 Small portion beef or lamb, lamb chop, fish, white meat of chicken
  (not fried).
 Boiled, baked, or mashed potato.
 Asparagus, carrots, string beans, spinach, tomatoes or peas.
 Stewed fruit without skin or seeds as pears, peaches, applesauce, ripe
  bananas, custard, junket, or jello.
 White bread or toast with butter or jelly.
 Buttermilk, thin cocoa, or tea.

Supper
 Milk soup with strained vegetables or clear soup.
 Egg, soft or hard boiled or poached.
 Small portion cream cheese or pot cheese or well-cooked cereal
  with milk and sugar or strained vegetable as above.
 Stewed fruit without skin or seeds as pears, peaches, applesauce, ripe
  bananas, custard, junket, or jello.
 White bread or toast with butter.
 Buttermilk, thin cocoa, or tea.

In some patients, particularly those with atonic colons,
lax abdominal walls and sluggish motility, the addition of
bulk is essential to success. In such instances, to ascertain the
effect, it is advisable to administer a teaspoonful of refined
psyllium seed preparation or Karaya gum in a glass of water
from one to three times daily. The addition of *"roughage"
foods* to the diet often irritates the gastric and intestinal
mucosa. However, they may be tried cautiously. Among
such "roughage" foods are apples, prunes, figs, pears, peaches,
grapes, bananas, cabbage, cauliflower, celery, Brussels sprouts,
corn, broccoli, rhubarb, lima and kidney beans, rye bread,
wholewheat bread and bran.

ANTISPASMODIC DRUGS.—Theoretically, such drugs are
highly desirable. I prefer *phenobarbital* (grain ⅛ t.i.d., a.c.)
plus *atropine sulfate* (grain ¹⁄₁₅₀ t.i.d., a.c.) or *syntropan*
(mg. 50 t.i.d., a.c.).

LAXATIVES.—A mild *saline laxative*, such as sodium phosphate, Epsom salt, Glauber salt, or Carlsbad salt, 1 teaspoonful in a glass of hot water on arising, is best. Mineral oil (with or without a little agar, such as Petrolagar), 1 or 2 tablespoonfuls before retiring, is excellent. *Irritant laxatives* are needed (1) for the aged with flaccid abdominal walls, (2) after pregnancy and abdominal operations, and (3) when nonirritant laxatives fail. Irritant laxatives include cascara sagrada (5 grains nightly), castor oil (1 teaspoonful of tasteless castor oil in 1 tablespoonful of mineral oil), or milk of magnesia (1 to 3 tablespoonfuls at night).

ENEMAS; IRRIGATIONS.—Enemas are very useful and are the best form of therapy for dyschezia. The following are recommended: (1) normal saline or 1 per cent bicarbonate of soda; (2) olive or cottonseed oil (3 ounces before retiring); (3) the watery enemas should not exceed 1½ quarts (lukewarm, allow to run in until a cramp is produced, then expel and repeat). A daily enema the first week, then alternate days for another week is a good form of therapy at the onset of the treatment.

Colonic irrigations are only occasionally indicated. They are useful when there is considerable "intoxication," good in the severe stages, and particularly important in the atonic cases. They must be given with care or the defecation reflex will be lost. Normal saline or 1 per cent bicarbonate of soda is best.

REGULAR BOWEL HABIT.—The institution of a regular "bowel habit" is of paramount importance. The best time is after breakfast. If there is no movement in three minutes, a glycerin suppository may be used and if this is without result, a hand rectal bulb syringe (1 to 3 ounces) of warm water may be injected. This procedure should be continued for two weeks, after which the defecation reflex is usually restored.

B. ACIDOPHILUS IMPLANTATION.—The implantation of B. acidophilus has been advocated. It is claimed that fermentative organisms (producing only lactic acid and carbon dioxide) are preferable in the bowel to putrefactive organisms (producing toxic amines, etc.). The implantation is done by

drinking fresh cultures or by rectal instillations. The normal flora of the colon consists of B. coli and the enterococcus. In most cases of spastic constipation, there is small intestinal hypermotility and, therefore, the food residues entering the colon depend on the diet. A predominantly carbohydrate diet produces gram-negative organisms. Lactose (1 to 4 teaspoonfuls daily) and acidophilus milk or viable cultures help this process. A fair amount of protein in the diet increases the number of gram-positive (enterococcus) organisms. The problem resolves itself into three factors: (1) lessening the small intestinal motility—atropine does this, trasentin also helps and small doses of opium may be used; (2) changing the diet to a high carbohydrate, low protein formula is necessary; (3) lactose and B. acidophilus may be added. Since the entire question of "intestinal intoxication" is disputed, this subject is as yet unsettled and a careful evaluation of the results of this form of therapy is not at hand.

B. Coli Implantation.—The rectal implantation of laboratory strains of B. coli has been recommended (E. Libman). The patient may be poisoned by his specific B. coli toxin. The presumably nontoxic laboratory strains may supplant the patient's own toxic B. coli strain. Strikingly good results are seen occasionally.

Physical Therapy.—Physical therapy has been practiced in chronic constipation. *Abdominal massage* is used—alternate hot and cold applications on the abdomen are advised. *Short wave diathermy* for the spastic sigmoid seems good. Physical therapy is probably not very important in the therapeusis of constipation.

Course of the Therapy

After two or three weeks the enemas may be discontinued or reduced to one a week, the salts may be given every other morning, and the amount of mineral oil reduced. The diet may gradually be increased to a normal one or even to the inclusion of roughage depending on circumstances. Should food roughage be irritant to the stomach it is possible to use either agar-agar or some form of vegetable gum. The use of *bran* for purposes of increasing the cellulose content of the

stool seems to be contraindicated, since experimental evidence has shown that the cellulose particles in bran are rough and tend to produce irritation of the colonic mucosa.

In the majority of patients with chronic constipation these measures will lead eventually to a cure, and most of the drug and dietetic measures may be discontinued. It is then possible in many patients by the use of mineral oil nightly or every other night and a warm alkaline drink, such as ½ teaspoonful of bicarbonate of soda in a glass of hot water on arising, to regulate the bowel movement.

Certain other measures, such as the use of *vitamins*, have been advocated. Vitamin B₁ particularly has a definite effect on improving the muscular tone in the colon. One should also always investigate the ductless glandular system carefully. Mild degrees of hypothyroidism are known to produce chronic constipation, and in these cases *thyroid extract* alone gives excellent results. Some patients are greatly benefited by *exercise of the abdominal wall*, and for patients with ptosis the use of properly fitting *abdominal binders* is of value.

When chronic constipation does not respond to the kind of treatment outlined, careful examination will usually reveal the presence of organic disease. In a few failures that we have encountered with these methods, patients have had chronic appendicitis with adhesions and the constipation has disappeared with removal of the appendix. Others have had undiagnosed peptic ulcer or chronic gallbladder disease.

CHRONIC DIARRHEA

DEFINITION.—One may define diarrhea as a condition in which the bowels move more frequently than once a day and there is a thinner consistency of the stool than normal, varying from watery to mushy. The reason for the thin consistency is that the rapid passage through the bowel does not give sufficient time for either the right or left portion of the colon to absorb the water. It is possible to have a diarrhea with formed stools but on close examination these cases are usually found to be instances of fragmentary constipation.

One should distinguish sharply between the inflammatory

and the noninflammatory types. In the inflammatory type, abnormal elements such as mucus, pus and blood are present. The presence of mucus alone may or may not be associated with an inflammatory condition.

Stercoral Diarrhea

Stercoral diarrhea occurs, paradoxically, in a patient with chronic constipation in which the hardness of the stool irritates the mucous membrane. As a result of the irritation there is an occasional attack, lasting one or two days, of abdominal cramps with frequent watery bowel movements, at times containing mucus and blood. The stools may at first be scybalous and then change to a watery consistency.

This is not an uncommon type of diarrhea. The *treatment* of acute attacks consists of heat to the abdomen, instillation of oil, and enemas and the use of antispasmodics such as syntropan or atropine, and even opium may be necessary for the severe cramps.

Gastrogenous Diarrhea

Achlorhydria and subacidity are associated in the majority of instances with normal bowel movements or constipation. Approximately one third of the patients with achlorhydria and subacidity have a gastrogenous diarrhea. This type of diarrhea includes most of the cases described by Adolph Schmidt as "putrefactive intestinal dyspepsia."

The occurrence of diarrhea in patients with achlorhydria or subacidity is not completely understood, but the following factors play a role: there is in these conditions less disinfection of the swallowed bacteria; the hydrochloric acid control of the pyloric sphincter from the duodenal side is absent, and the food is not as well liquefied or prepared for subsequent digestion as in stomachs with normal acids. This diarrhea may occur in patients with low gastric acidity as well as in those with complete achlorhydria. It is not due to inflammation of the colon, nor does it, even after many years, lead to inflammation of the colon. Mucus and blood are not seen in the stools. Patients with gastrogenous diarrhea have a few bowel movements on arising and particularly after the

stool seems to be contraindicated, since experimental evidence has shown that the cellulose particles in bran are rough and tend to produce irritation of the colonic mucosa.

In the majority of patients with chronic constipation these measures will lead eventually to a cure, and most of the drug and dietetic measures may be discontinued. It is then possible in many patients by the use of mineral oil nightly or every other night and a warm alkaline drink, such as ½ teaspoonful of bicarbonate of soda in a glass of hot water on arising, to regulate the bowel movement.

Certain other measures, such as the use of *vitamins*, have been advocated. Vitamin B_1 particularly has a definite effect on improving the muscular tone in the colon. One should also always investigate the ductless glandular system carefully. Mild degrees of hypothyroidism are known to produce chronic constipation, and in these cases *thyroid extract* alone gives excellent results. Some patients are greatly benefited by *exercise of the abdominal wall*, and for patients with ptosis the use of properly fitting *abdominal binders* is of value.

When chronic constipation does not respond to the kind of treatment outlined, careful examination will usually reveal the presence of organic disease. In a few failures that we have encountered with these methods, patients have had chronic appendicitis with adhesions and the constipation has disappeared with removal of the appendix. Others have had undiagnosed peptic ulcer or chronic gallbladder disease.

CHRONIC DIARRHEA

DEFINITION.—One may define diarrhea as a condition in which the bowels move more frequently than once a day and there is a thinner consistency of the stool than normal, varying from watery to mushy. The reason for the thin consistency is that the rapid passage through the bowel does not give sufficient time for either the right or left portion of the colon to absorb the water. It is possible to have a diarrhea with formed stools but on close examination these cases are usually found to be instances of fragmentary constipation.

One should distinguish sharply between the inflammatory

type rarely. Professor I. Snapper has informed me personally that it is quite common in Holland.

Adolph Schmidt divided this colonic type of dyspepsia into two groups: the putrefactive intestinal dyspepsia and the fermentative intestinal dyspepsia. In modern times it has been the tendency to describe these disturbances in the colon under the heading of "simple colitis" or "irritable colon." However, these patients have no inflammation of the colon and the term "colitis" should be dropped. The expression "irritable colon" is also unscientific. All living tissue is irritable. It is probable that there exists a large group of patients with functional disturbances in the gastro-intestinal tract who suffer either from constipation or diarrhea. Where the disturbance is primarily a nervous dysregulation of the secretory and motor activities in the gastro-intestinal tract, this may be part of a hyperirritability or imbalance of the vegetative nervous system. The term "hyperirritability of the gastro-intestinal tract" or a "hyperirritable gastro-intestinal tract" may be applied to these conditions.

My personal experience has led me to think that the chief disturbances in this condition consist in an increase or decrease of the secretory and motor activity of the stomach with a hypermotility or rush through the small intestines. What the disturbances in the secretory activity of the pancreas or intestine and bile are in these cases is as yet unknown. It is very common to see in patients with functional disturbances in the colon, either in constipation or diarrhea, a rapid passage of the barium meal through the small intestine. As a result, partially digested and some undigested food appears in the colon. Depending on the diet of an individual, carbohydrates or protein will predominate in this residue offered to the colon. The result of the presence of these foodstuffs in the colon will be a predominance either of the aciduric group of organisms, including the acidophilus bacilli because of the large carbohydrate content, or, an increase of the putrefactive organisms, if protein predominates in the diet. Furthermore, the nervous factors may produce changes in the motility and tone of the colon so that either spastic constipation or diarrhea of one type or another may result.

partaking of food. The stools are characteristic—small, dark, foul, alkaline—and often reveal undigested meat fibers.

The *treatment* in this type of case consists in the use of a nonresidue diet, enemas and constipating drugs such as bismuth subcarbonate or kaolin in teaspoonful doses three times a day after meals. The specific remedy is *hydrochloric acid and pepsin*, administered after meals, the dosage depending on the examination of the stools for digested meat fibers after the use of the acid-pepsin mixture. Usually 10 to 20 drops of dilute hydrochloric acid is sufficient. In severe cases, it may be necessary to give one, two or three times daily, a moderate amount of deodorized tincture of opium, 5 to 10 drops, in order to control the diarrhea.

Some cases of gastrogenous diarrhea are quite refractory to the usual therapy. In such instances, intramuscular injections of *crude liver extract* (to improve the gastritis which is presumably the cause of the subacidity) are often of great value.

Intestinal Fermentative Dyspepsia

In intestinal fermentative dyspepsia the patient has from two to four bowel movements a day. The condition persists for years. The symptoms are slight. There is some abdominal distention with rumbling of gas and the expulsion of large quantities of flatus. The patient may have slight colic or dull abdominal pain. The stool is characteristic. It is rather bulky, of a light color, sour and gassy, and acid in reaction. When it is stained with iodine, one sees large masses of starch in the microscopic examination.

The *cause* of this peculiar chronic fermentative diarrhea is unknown. The pancreatic function seems normal in these cases. Starch is digested by the diastases of the saliva, pancreas and intestines. If these ferments are deficient, starch enters the colon and the colonic diastase converts it into sugar. The sugar is then fermented by the bacteria with the production of carbon dioxide and organic acids such as acetic and lactic acids. It is the opinion of Hurst that the deficiency of the other diastases together with the presence of colonic diastase is responsible for this disease. We see this

the use of *nerve sedatives* such as phenobarbital or bromides; the use of the heavier *astringents* such as bismuth subcarbonate or kaolin, and possibly aluminum hydroxide; the use of *antispasmodics* such as atropine and syntropan; the use of *vegetable gums* (here I would like to call your attention to an inexpensive preparation known as "Carob Gum" which is obtained from St. John's bread. It may be prescribed in doses of 1 teaspoonful three times a day. It should be prepared by adding the powder to ¼ glass of cold water and then filling the tumbler slowly with boiling water. This solution is taken lukewarm once, twice, or three times a day between meals); the use of *opium* preparations either in the form of extract of opium, ¼ grain, one, two or three times a day, or deodorized tincture of opium, 5, 10 or 15 minims once, twice, or three times a day; and finally, the use of cleansing and soothing *enemas*, or colonic irrigations, employing warm saline and warm 1 per cent bicarbonate of soda.

Nervous Diarrhea

Another type of diarrhea is the nervous type. While patients may suffer with chronic diarrhea as a result of nervous or psychic factors, one should investigate very carefully for the presence of an inflammatory colitis. These nervous patients, usually women, remain at home and refuse to go out into society. They often become addicted to constipating drugs, particularly opium. Diarrhea is associated psychologically with fear and also forms in some infantile reversion states an equivalent of sexual gratification. In these patients, the psychological approach is best. Nevertheless, the general measures described under "Therapy" may be necessary.

Diarrhea in Exophthalmic Goiter

In Graves' disease, the diarrhea may be due to a gastric or pancreatic achylia or to a toxic influence on the colon, but it is also frequently associated with psychic factors. A psychic disturbance in a patient with Graves' disease seems to lead very easily to attacks of diarrhea. The best treatment here, of course, is subtotal thyroidectomy.

Allergic Diarrhea

Still another type is the allergic diarrhea, formerly called "anaphylactic diarrhea." Certain foods are particularly prone to produce allergic diarrhea. These are strawberries, sea food, fish, eggs and milk. The patients may have, in addition to the diarrhea, nausea, vomiting and fever, and various types of erythema.

One-half to 1 mg. of epinephrine may relieve the symptoms. The diagnosis depends on the history, skin tests, and what is probably the most valuable measure, elimination diets. Therapeutically, one must eliminate the offending allergens. Desensitization, commencing with minute amounts of the allergen and gradually increasing the amount, may be attempted, but usually fails.

Treatment of the Diarrheas

Therapeutic measures employed in the diarrheas include a *nonresidue diet* such as the one given under "Constipation";

SPASTIC COLON

WILLIAM HARLEY GLAFKE, M.D.*

Spastic colon is a condition of the bowel characterized by such local symptoms as irregular bowel action, abdominal distress or pain, excessive gas and variable appetite; and such general symptoms as weakness, fatigability, insomnia, faint feelings, depression and nervousness. It is not a sharply defined entity. It may occur alone, or it may occur in connection with other digestive or systemic diseases. It has been known by various names, such as "mucous colitis," "intestinal indigestion" or "irritable bowel."

ETIOLOGY

Spastic colon is a condition of adult life rather than of childhood, and affects both sexes about equally. Especially does it occur frequently in individuals living under *stress* or *tension*. Professional workers, teachers and executive heads in business are common sufferers—as are also individuals bearing too great a burden, such as children supporting aged or ill parents, or wives supporting stricken husbands, or widows raising children under financial difficulties. *Nervous fatigue* is usually an underlying causative factor. Fear of failure, fear of loss of position, fear of financial insecurity, fear of ill health, fear of criticism—all are causes commonly met with when taking the histories. Another large group of patients have slipped into the condition by following food fads which have led to unbalanced diets, or by the *abuse of cathartics* when trying to rid themselves of "auto-intoxication."

SYMPTOMATOLOGY

Local Symptoms

Gas.—This takes the form of belching or abdominal distention, or excessive passing of flatus. There is a feeling of

---

* St. Luke's Hospital.

Stomach Symptoms.—Anorexia, regurgitation of stomach contents, heartburn, nausea and even vomiting are common gastric symptoms. The appetite is fitful. Often a patient states that he would like to eat but is afraid of the ensuing distress.

General or Systemic Symptoms

Nervousness.—This word of many meanings, as used by these patients, may express irritability, apprehension, excitability, lack of concentration, restlessness, a desire to "jump out of my skin," "weepiness," and general depression.

Insomnia, or troubled, restless sleep with much dreaming are frequent complaints. The abnormal colonic activity is reflected in nightmares, or may be painful enough to prevent sleep entirely.

Fatigability.—There seems to be some close connection between a sense of fatigue and this overacting colon. On days when there is diarrhea, these patients are listless and lack all desire to do anything, or are quickly fatigued if they try. They have a sense of not caring "whether school keeps or not," and feel futile and frustrated. Within a day or two, if the colon is brought back to a quiet condition, these symptoms will often disappear and the normal "drive" comes back to allow our patient to accomplish his daily tasks.

Vasomotor Reactions.—In this group of patients, we frequently see a very distressing syndrome. Just preceding, or just following a loose diarrheal movement, the patient feels a sudden complete exhaustion with faintness. He breaks out in cold perspiration. He is nauseated. He has extreme palpitation of the heart, with perhaps a fast, weak pulse. He becomes pale, and his one desire is to lie down, lest he "pass out" completely. With rest for perhaps a half hour, the attack gradually terminates. This may be called a "colon reaction," and illustrates the close connection between local colon activity and general nervous stability.

Toxic Symptoms.—These patients complain of dull headache, or bad taste in the mouth, or "laziness," or inability to think clearly, and are prone to blame these symptoms on improper elimination. They worry about auto-intoxica-

fullness after meals. The clothing is actually tight about the abdomen, and there is much rumbling and gurgling through the intestines. It is truly remarkable how quickly and excessively abdominal distention will occur in some instances. A common complaint is the inability to pass off the gas rectally, or a feeling of smothering about the heart and a sense of cardiac oppression, which may throw the patient into a complete panic. On questioning, the patient states that immediate relief occurs if he can pass the gas rectally.

Pain.—Abdominal discomfort may range from mild uneasiness to extreme disabling pain. Pain is commonly colicky, cramplike, come-and-go in type, or may be steady, aching and boring. It is relieved (at least temporarily) by the passage of gas or bowel movement. It occurs in various parts of the abdomen, and may be felt to move from place to place accompanied perhaps by gurgling sounds. It is commonly felt in the lower back. It occurs at any time of day or night. In contradistinction to ulcer pain, it is not relieved by eating, but, on the contrary, may be made worse by the taking of food. A frequent time for the pain to occur is from 3 to 5 A. M., when it wakens the patient and may prevent sound sleep the balance of the night.

Abdominal Tenderness.—The colon is often palpable and tender to pressure, and is at times felt as a contracted cord which can be rolled under the examining hand.

Irregular Bowel Action.—This group of patients run the gamut between constipation and diarrhea, and these may alternate in the same patient. It is well to elicit just what a patient means when he speaks of constipation. He may mean that he does not have any movement at all for a day or two— or he may mean that on occasions the stools when passed are hard and ball-like. In some cases of "alternating constipation and diarrhea," the actual condition is really diarrhea, since all stools actually passed are loose or watery and the "constipation" is simply the hiatus of one to two days between diarrheal passages. Frequently in "spastic colon" it is noted that the bowels move before breakfast rather than at a more normal after-breakfast time. There may be one or many stools during the day.

Clostridium welchii group of organisms. Positive cultures of Cl. welchii are most frequent in the "gassy" stools.

Gastric Analysis

A test of stomach contents is always indicated. In a small percentage of cases, a deficiency of hydrochloric acid will be found, and will give a clue to special treatment. No characteristic level of hydrochloric acid is found, but it is often high, as is common in this nervous type of individual.

Blood Study

The blood picture is frequently of mild anemia but this is not diagnostic. The presence of high eosinophilia will often raise the suspicion of some allergic factor, or of infestation.

X-ray Examination

A gastro-intestinal series of films should always be made, combined with barium clysma. Characteristically, the colon in part or as a whole will show deep haustrations, and the twenty-four-hour film will give the "coral bead necklace" appearance.

Fluoroscopically, the barium enema will show areas of spasm, finally yielding to gentle pressure of the ascending column. After evacuation, frequently there is a feathery appearance to the colon caused by tiny particles of barium which have adhered to the colon wall.

Proctoscopic Examination

The proctoscopic examination reveals simple congestion of the colonic and rectal membranes, with adhering patches of mucus. Rectal examinations should always be made in order to rule out ulceration, polyp, tumor and bleeding. All too many rectal cancers have been overlooked because of neglecting this simple procedure.

DIFFERENTIAL DIAGNOSIS

In diagnosing "spastic colon" extreme care must be given to the differential diagnosis. *Gallbladder disease* must be ruled

tion, are constantly overemphasizing the elimination of "poisons" from the system, and dwelling too much on whether the bowel action is "adequate," fearful lest the colon be "clogged up." Many of them follow bizarre ideas of diet—ideas which they have accumulated from reading the many food fad books and magazines, or from believing all the advertisements for cathartics which they read in the public press—or which they hear over the radio. At times this preoccupation with proper elimination becomes an actual obsession. A majority of them have taken all sorts of cathartics over the years or months of their trouble, and by this self-medication have added more and more to colonic irritation.

DIAGNOSIS

Laboratory Data

Examination of Stools.—The examination of stools is of great aid in the diagnosis. Characteristically, the presence of *mucus* is the outstanding abnormality—and it occurs either as finely divided mucus, or as coarse flakes or webs. The finely divided shreds of mucus are most easily seen grossly by smearing the stool around the inside of its glass container and then looking through it toward an adequate light. The mucus will look like small particles of white of egg adhering to the glass. The coarser mucus will be in large masses covering the more solid portions of stool, or will be passed in masses of gelatinous character entirely independent of feces. Long strings of mucus strongly resembling worms are sometimes passed, and cylindrical "casts" of the bowel, composed of thick tenacious mucus, may be noted.

Grossly, also, the stool may contain many undigested fibers of vegetable, fruit, or meat. The stool as a whole is loose, mushy—even watery—or may be spongy and quite apparently full of gas pockets. The odor varies with the type of diet the patient has been following; it may be putrefactive or fermentative, and is always more malodorous than the normal well-digested solid stool. For microscopic data on these stools, the reader is referred to any good laboratory manual. Cultures of stools, especially anaerobic cultures, help greatly in some cases by showing excessive numbers of the

place through the involved and complicated mechanism of propulsive and segmentative peristalsis, which exposes the food to the villous absorptive surface of the small intestine. Finally, still as a liquid, the residue is poured into the cecum and right colon. It is now devoid of any further food values, and is ready to be eliminated from the body, the "chaff" after the "wheat" has been separated.

Colonic function from now on is a combination of dehydration and expulsion. In the ascending colon and a portion of the transverse colon, absorption of water slowly takes place until the mass is partly dehydrated. Then this mass is moved rather quickly in "rushes" to the descending colon and sigmoid, where gradually and slowly again dehydration continues until a formed compact fecal mass results. When this mass reaches sufficient bulk to "trip the trigger" of peristaltic action, the sigmoid passes the stool into the rectum, and it is extruded by rectal contraction and anal relaxation. Normally the stool is soft enough to pass easily but firm enough to retain its cylindrical shape, and is compact enough to sink in water. It has been variously described as "cigar-shaped"—or of the consistency of butter at room temperature.

It is at once evident from these facts that if the propulsion of the fecal material through the colon is too swift, insufficient time for dehydration is allowed and the stool will be loose or liquid. On the contrary, if the propulsion is too slow, too much dehydration will occur and a hard ball-like stool will result. It also follows that if the stool is of normal consistency, the bowel is moving at the right rate, whether it be once a day—several times a day—or once in two or three days. *It is not the frequency of bowel movement which determines normality, but rather the consistency of the stool actually passed.*

The inside factor which stimulates the colon to act is the presence of bulk or residue in the right colon. In general, the rule holds that the greater the bulk, the greater the activity. The normal individual eating a mixed diet has sufficient residue from his vegetables and fruits to cause just enough peristaltic action to push this residue forward at the right rate so that a normal stool results.

out by history, duodenal drainage and cholecystography. As it frequently occurs in the same patient with "spastic colon," the differentiation is difficult. The *specific dysenteries*, such as amebiasis and bacillary dysentery, are identified by their stool cultures and examinations, their temperature records, and presence of blood or pus or both in the feces. *Diverticulosis* is manifest by the x-ray. *Malignancy of the colon* shows itself in the x-ray film, by proctoscope, blood in stools and by the age incidence. *Pernicious anemia* is identified by careful blood counts and by lack of free acid in the test meal. *Sprue, pellagra, brucellosis, infestation* with Ascaris, hookworm, tapeworm—all of these must be given thought and ruled out by proper tests.

Allergy of the gastro-intestinal tract has separated a large group from the former boundaries of "mucous colitis" or "spastic colon." Elimination diets give enormous information at times, as do local skin tests. *Endocrine disorders* like hyperthyroidism must be considered and tested for. It is evident that "spastic colon" is a diagnosis that is made only after much careful consideration, painstaking elimination and prolonged observation.

PHYSIOLOGIC CONSIDERATIONS IN TREATMENT

Before discussing the treatment of these patients, it will be well to review some of the fundamentals of *physiology of the gastro-intestinal tract* which underlie the treatment. Two main groups of factors influence the bowel: those affecting the bowel from the *inside* (namely, foods or other ingesta); and those coming to the bowel from the *outside* (namely, the nerves which control the bowel).

Factors Affecting the Bowel from the Inside

Naturally the inside factors are mainly food, but must include laxatives and other locally acting medicaments. Food is taken into the stomach, a mixture of liquid and solid. By addition of the gastric juice, with its chemical and enzymatic effects, the food becomes liquid before leaving the stomach. Thus it has been prepared for assimilation in its passage through the small intestine. The actual assimilation takes

parasympathetic nerves are most often at fault in being too active; that is, there is too much "drive." *Emotional disturbances* seem to result in a greater irritability or a lowered threshold of the vagus group. One can conjecture about this matter from many angles. If these patients are fundamentally ruled by fear, and fear in turn stimulates the adrenals, and if the adrenals are stimulating to the sympathetic system, may we not, after all, be dealing with too much "brake" rather than too much "drive"?

TREATMENT

Bland Diet

With the physiological background of spastic colon in mind, it is evident that in its treatment whatever food or medication enters the digestive tube should be of a non-irritating and soothing type. The bland or "smooth" diet is used at the beginning of treatment. Eggs, meats, fish, fowl, shellfish, soups, milk, buttermilk, cheese, "white" cereals (rice, farina, cream of wheat), white breads, white crackers, macaroni or spaghetti, sponge cake, angel food, custards, puddings (such as rice, tapioca, or corn starch), gelatins, potatoes, bananas, avocado pear, fruit juices, tea, coffee, and cocoa—these form the basis of the diet on which the patient starts.

No coarse breads, no vegetables either cooked or raw, and none of the fruits either cooked or raw are allowed because of their cellulose ("roughage") content. Excessive sugars, such as honey, molasses, maple syrup, fudge sauces, heavy frostings on cakes, and candies, are avoided because of their tendency to increase fermentation. Nuts, spices, condiments and pickles also are offenders. However, it makes little difference in this group of cases whether foods are fried, broiled, or baked. Allowing properly fried foods often removes one of the bugaboos that the patient has, and widens his choice of foods to advantage.

"Bulk Producers"

With the bland diet as given, the residue in the colon is at a minimum and some means must be found to stimulate

Time Table of Digestion.—An explanation of the "time table" of the passage of food from stomach to anus helps many patients to understand their physiology and to overcome their fears of "improper elimination." Food eaten yesterday as three meals, breakfast, lunch and dinner, was passed through stomach and small intestine during yesterday and last night, and its residue is being poured into the right colon this morning. During today and tonight the colon will move this residue, at first slowly, to the ascending colon and hepatic flexure—then later, by "rushes" into the left colon and sigmoid. Here it will be gathered together as a mass and will be passed as tomorrow's movement.

The colon is never normally empty. One day's stool is in the rectum while the next day's stool is in the cecum and ascending colon. If a cathartic is taken tonight on retiring, it hastens the whole process in the small intestine—strikes the colon early tomorrow morning—causes the colon to act faster than normal, and when the bowel movement does occur, it is the combination of tomorrow's stool with the next day's stool. The patient is gratified by the large and "satisfactory results," little realizing that it is really two days' movement. If, on the next day, the bowel does not move because it has not had time to "catch up," our patient is likely to resort to another cathartic because he is "constipated." Many patients thus start the pernicious habit of daily cathartics.

Factors Affecting the Bowel from the Outside

Turning now to the factors coming to the colon from the outside, we meet with the complex *nervous mechanism* which controls its activities. In a broad sense, it may be said to be a combination of "drive" (vagus or parasympathetic) and "brake" (the sympathetic system). When the two are in proper balance, normal peristalsis proceeds quietly and painlessly, and we are completely unconscious of any digestive activity. If, however, the "drive" is too great we can have overactive peristalsis with diarrheal tendency, or paradoxically, such spasticity and overcontraction of the colon that no propulsion occurs, and "spastic constipation" results.

It seems probable that in "irritable colon" patients, the

parasympathetic nerves are most often at fault in being too active; that is, there is too much "drive." *Emotional disturbances* seem to result in a greater irritability or a lowered threshold of the vagus group. One can conjecture about this matter from many angles. If these patients are fundamentally ruled by fear, and fear in turn stimulates the adrenals, and if the adrenals are stimulating to the sympathetic system, may we not, after all, be dealing with too much "brake" rather than too much "drive"?

TREATMENT

Bland Diet

With the physiological background of spastic colon in mind, it is evident that in its treatment whatever food or medication enters the digestive tube should be of a non-irritating and soothing type. The bland or "smooth" diet is used at the beginning of treatment. Eggs, meats, fish, fowl, shellfish, soups, milk, buttermilk, cheese, "white" cereals (rice, farina, cream of wheat), white breads, white crackers, macaroni or spaghetti, sponge cake, angel food, custards, puddings (such as rice, tapioca, or corn starch), gelatins, potatoes, bananas, avocado pear, fruit juices, tea, coffee, and cocoa—these form the basis of the diet on which the patient starts.

No coarse breads, no vegetables either cooked or raw, and none of the fruits either cooked or raw are allowed because of their cellulose ("roughage") content. Excessive sugars, such as honey, molasses, maple syrup, fudge sauces, heavy frostings on cakes, and candies, are avoided because of their tendency to increase fermentation. Nuts, spices, condiments and pickles also are offenders. However, it makes little difference in this group of cases whether foods are fried, broiled, or baked. Allowing properly fried foods often removes one of the bugaboos that the patient has, and widens his choice of foods to advantage.

"Bulk Producers"

With the bland diet as given, the residue in the colon is at a minimum and some means must be found to stimulate

colonic peristalsis. Cathartic drugs, such as cascara, phenol-phthalein, senna, magnesia and salines, must be strictly avoided since they irritate the mucous membrane of the colon much more than would the foods that have been omitted from the diet. But the various "bulk producers" may be used safely because they act in a physiological way, and are non-irritating to the membrane. They have the common property of absorbing water in the stomach to form gelatin-like masses which mix with the food in the passage through the small intestine. They are not absorbed, however, but are discharged into the right colon to form the bulk which is needed to initiate peristaltic activity. As they pass through the colon their physiochemical composition allows them to retain their moisture and give the stool a soft, easily molded consistency. They act—not as a drug—but by mechanical means and therefore do not "wear out" in their effect. They can be used indefinitely without leading to congestion or injury of the colonic lining.

Examples of bulk producers are agar-agar, in finely powdered form, in flakes, or in cereal-like form; derivatives of psyllium seeds, such as Metamucil, Konsyl and Mucilose; Kabaya preparations, such as Kaba, Siblin and Mucara. The usual dosage of these various products is 2 to 3 heaping teaspoonfuls a day. If the entire amount is taken in one dose, a feeling of some fullness may follow, hence it is best to give two or three smaller doses spaced through the day. Patients vary in the amount needed to secure bowel action, and large doses may be used without fear. Mineral oil has been widely used as a means of combating the hard scybalous stools, and when used in small doses is of great help. However, it should not be depended upon alone to get bowel action, as it interferes somewhat with food assimilation and with absorption of some of the fat-soluble vitamins.

Additions to Diet; Drugs

The patient is kept on this regimen of diet plus bulk producer for a variable period depending on improvement. Many patients have to remain on the bland diet more or less indefinitely, and in that case vitamins must be given sep-

arately to prevent deficiencies. As the gas, abdominal pain and local discomforts subside, additions are gradually made to the diet. First, coarse breads and cereals, then the milder cooked vegetables and cooked fruits, later raw vegetables (salads), and finally raw fruits are used to build up the diet. We aim to have the broadest diet that the patient can tolerate. If, for instance, an addition of vegetables is made too soon and increased discomfort results, we step back to the blander level for a week—or a month—more, and then try the addition again. The constant aim is to have the colon act with just that speed that results in the formed, normal stool. If the stools are loose and frequent, we reduce the amount of bulk producer, or the amount of roughage in the diet.

Drugs used for their effect inside the bowel include calcium carbonate, kaolin, colloid alumina, and preparations such as Kaomagna—bismuth subnitrate. Rectal instillations of olive oil or mineral oil are of help if hemorrhoids or fissures are a complication. Enemas should be used to give temporary help for constipation. For these, normal saline is preferable to soapsuds, and small amounts—1 to 2 pints—are less irritating than large amounts. Colonic irrigations except as an occasional temporary measure are to be avoided.

Treatment of the Nervous Element

Considering now the influences that affect the colon from the outside, we must treat the nervous elements of the patient's problem. Sympathetic discussion of his emotional situation is of extreme help. Allowing a patient to pour out his worries, his hurt feelings, or his resentments will give him relief and comfort. At times, it will be possible to give actual help in adjustment of some of his difficulties. Reassurance as to the unimportance of various phases of his illness, explanation of his symptoms, so that fear as to what they might mean will be allayed, and simple elucidation of the physiological background for the diet and medication will gain his confidence and assure enthusiastic cooperation. Adjustment of his routine of work so that more time is given to relaxation or hobbies is a part of re-educating the patient to meet his responsibilities without apprehension. Attention must be given

to sleep habits, and sedation should be used if necessary. Above all, allaying of fear, and reassurance, are the fundamentals in helping these people to a more normal attitude toward life.

Specifically, certain "digestive" fears are commonly met with in these patients. One is the fear of being poisoned by retained feces, the fear that if daily evacuation does not occur, dire ill health will result. This may be combated by explaining that the normal colon is lined by a membrane which is protective and absorbs practically nothing but water—and which acts as a barrier between the products of fermentation and putrefaction, inside the colon, and the blood stream outside. By explaining, further, that the whole object of our treatment is to restore the colon wall to a normal state by soothing diet and medication, we get from our patient a more complete cooperation.

The patient must be reassured that, although during the first few days or weeks of his treatment he may have many distressing symptoms of gas, abdominal pressure, even pain, and the bowels will not move regularly, this stage is a preliminary through which he must go to reach the more comfortable stages later. In following these cases from week to week, it is common to have a patient report, at the end of the first week that the bowel has moved daily and very satisfactorily. At the next report, a week later, however, discouragement has developed because the bowel has moved irregularly or only with some such help as with an enema. The fear enters the patient's mind that the diet, or the bulk producer, has "worn out." The explanation should be made that the colon during the first week was still so irritable and "touchy" from the previous cathartics or rough diet that it reacted to the amount of bulk producer used. By the second week it had recovered enough so that its irritability was lessened, and more bulk was needed to cause evacuation. A simple increase in the amount of bulk producer, or addition of some of the rougher foods is usually all that is needed to correct this phase.

Another common fear is that the bowels are not moving enough—that the stools are not large enough considering the

meals eaten. The answer is that these patients have been having loose watery stools, either from cathartics or rough diet, and are expecting too much, now that the stool is compact and free of fluid.

The *drugs* that are helpful in the nervous control of these cases are: (1) sedatives such as phenobarbital, bromides, or even codeine or morphine; (2) antispasmodics, such as tincture of belladonna, atropine, trasentin, syntropan, novatropin, calcium gluconate, and opium derivatives such as paregoric, or even laudanum. Other measures are heat to the abdomen, by hot water bag, by electric pad, or by diathermy.

The outlook for improvement in spastic colon, if it is treated patiently and persistently, is definitely good. The course will be irregular—some weeks better, some not so well—and the element of time must be emphasized to the patient. He should be reassured as to final results, but should be told that weeks rather than days should be his measure of improvement. Each case is of course a different problem, with varying emphasis put on various symptoms. But with a proper understanding by both physician and patient of the physiology of the digestive tube, and by stressing the neurological aspects of the condition, careful treatment will lead to gratifying success.

TUBERCULOSIS OF THE ALIMENTARY TRACT

H. McLEOD RIGGINS, M.D., F.A.C.P.*

ALTHOUGH tuberculosis of the terminal ileum and parts of the large intestine is probably the most frequent complication of advanced active pulmonary tuberculosis, the esophagus and stomach are rarely involved. Just why the ileocecal region is frequently involved and the upper alimentary tract rarely so, is still a subject of conjecture about which several theoretical explanations will be mentioned. Tuberculosis of the esophagus may develop by direct extension from the pharynx or larynx or from caseous tuberculous tracheobronchial lymphadenitis. While tuberculosis of the gastric mucosa is also extremely rare, it may occur as a result of ingestion of tubercle bacilli in patients with positive sputum. In 734 cases of fatal tuberculosis, Cullen[6] found at autopsy only four instances of stomach involvement. This low incidence of tuberculosis of the stomach agrees with the findings of most pathologists and clinicians.

While most of our knowledge of intestinal tuberculosis has accumulated since the beginning of the present century, it is of interest to glance briefly at the historical concepts of the disease before considering the evolution of present-day ideas. As in other fields of medicine, progress in this field was tediously slow until after the turn of the century. Hippocrates[10] Aretaeus,[2] Richard Morton,[13] Bayle,[3] Louis[11] and, more recently. Rokitansky[14] and others commented upon the occurrence of diarrhea in phthisical patients. Hippocrates[10] wrote that "Diarrhea attacking a person with phthisis is a mortal symptom." He was undoubtedly the first to mention that alternating constipation and diarrhea not infrequently

* Associate in Medicine, College of Physicians and Surgeons, Columbia University; Medical Director, Triboro Tuberculosis Hospital; Associate Visiting Physician, Bellevue Hospital.

occur in phthisical patients. Richard Morton[13] (1694) wrote in a most interesting way "Of a Consumption from a Bloody-Flux, and from a Looseness"—"Mr. Tindal's only Daughter, a very fine young Woman, but Scorbutical, and something Melancholick, about eighteen Years of Age, upon the Suppression of her Monthly Courses, fell into a Colliquative Looseness, with Stools that came away like Water, which by degrees brought her in the space of a Year into an universal Atrophy—in the Body, when it came to be opened after 'twas dead, the Lungs appeared full of little Swellings" (Morton[13]).

MODES OF INFECTION

Very little progress in the knowledge of intestinal tuberculosis was made from the time of Morton's[13] publication until Rokitansky's[14] classical work on the pathology of intestinal tuberculosis (1845). His work has been the basis largely of most subsequent studies of intestinal tuberculosis. He pointed out that "the presence of tubercle in the tissues of the intestinal mucous membrane and by extension in the deeper seated coats constitutes a most important disease—tuberculosis of the intestines in a broad, tuberculosis of the intestinal mucous membranes in the narrower sense. It may proceed to ulcerative destruction and thus establish genuine intestinal phthisis." He emphasized that it rarely occurs in the idiopathic form but is usually *secondary* to suppurative pulmonary tuberculosis.

Hematogenous tuberculosis of the intestinal mucosa is apparently extremely rare. The tendency for the lesions to occur especially in the ileocecal region and the frequent finding of tubercle bacilli in gastric lavage contents in patients with pulmonary tuberculosis is good evidence of the *ingestion* mode of infection. However, a considerable number of writers have favored hematogenous infection rather than ingestion of bacilli. As recently as 1940, Cullen[6] stated that the high incidence of intestinal tuberculosis in acute miliary tuberculosis indicates that the hematogenous route is more common than generally supposed. Cullen[6] failed to say whether or not his autopsy miliary cases developed pulmonary cavity and a positive sputum before death occurred.

On the contrary, Boles and Gershon-Cohen[4] found no intestinal tuberculosis in their cases of miliary and noncavitary fibroid tuberculosis. Gardner[7] has shown that animals infected by the hematogenous route may develop tuberculosis of the wall of the alimentary tract. Smith[15] also demonstrated that experimental animals on a regular diet, and ingesting tubercle bacilli, rarely developed intestinal tuberculosis, but when on a diet deficient in vitamins, they developed tuberculous enteritis readily and soon died. The great majority of evidence and opinion supports the ingestion mode of infection as the important and usual one.

INCIDENCE

The occurrence of tuberculous entercolitis is frequent, especially in patients who have had advanced active pulmonary tuberculosis for several years. The incidence depends largely upon the extent and character of the pulmonary disease, the Gaffky content of the sputum and the natural resistance of the patient. Tuberculous enteritis is more common in the colored race and is most common in that age group in which the morbidity and mortality of tuberculosis is highest. It is also more common in females than in males. Its demonstrable clinical incidence depends largely upon the diagnostic procedures used and the careful and repeated search for its presence.

Brown and Sampson[5] report finding 1465 instances of clinical intestinal tuberculosis in 5542 cases studied roentgenologically. Many of their patients had minimal pulmonary disease. In 1930 the same authors stated that intestinal tuberculosis is found at 50 to 80 per cent or more of all autopsies done on patients dead of pulmonary tuberculosis. They estimated that, of the 84,557 patients who died of pulmonary tuberculosis in the United States in 1927, 40,000 to 65,000 probably had intestinal tuberculosis.

Some investigators do not agree with Brown and Sampson regarding the incidence of clinical intestinal tuberculosis. However, the majority of those with extensive experience in this field agree that the incidence is high. The figures reported by different clinicians indicate that intestinal tuber-

culosis may be present in from 10 to 30 per cent of patients with active pulmonary tuberculosis. The differences in the reported frequency undoubtedly depend upon several factors, the most important being the type of patients studied, the stage and character of their pulmonary disease and the diligence for which intestinal tuberculosis is searched for, the criteria used in its diagnosis, and the methods of study. Cullen[6] found 734 cases or 70.4 per cent with tuberculosis of the alimentary tract in a series of 1043 autopsies of patients dead of pulmonary tuberculosis. In 190 cases of fatal pulmonary tuberculosis, Gardner[7] at autopsy found 85 per cent to have tuberculosis of the alimentary tract.

Effect of Increased Use of Collapse Therapy on Incidence. —Since the incidence of intestinal tuberculosis seems to vary with the duration of active advanced pulmonary disease and increases in proportion to this duration, and since most clinical studies including Brown and Sampson's were made prior to the era of intensive collapse therapy, and inasmuch as early satisfactory collapse of the diseased lung probably appreciably reduces the chances of prolonged intestinal infection, it is logical to suspect that the incidence of clinical intestinal tuberculosis in cases receiving prompt and satisfactory collapse is probably appreciably less than that found in advanced cases of tuberculosis ten or fifteen years ago when collapse therapy was used late and infrequently. A careful roentgenological and clinical study to determine the incidence of intestinal tuberculosis in patients having early and satisfactory collapse therapy would be of decided interest and value and should furnish important information regarding its value, in the broader sense. Should the incidence of intestinal tuberculosis be found materially less in cases having a satisfactory collapse, this "by-product" of satisfactory collapse should assume a more important place in the indications for *early* collapse than it apparently does at present. Not many years ago, intestinal tuberculosis was regarded as a contraindication to collapse therapy by many physicians. Today, intestinal tuberculosis is generally considered an indication for collapse therapy if the patient is otherwise suitable for this method of treatment. Parenthetically, early and satisfactory collapse

therapy may similarly be expected to reduce the incidence of other serious complications of pulmonary tuberculosis such as laryngeal and bronchial tuberculosis.

LOCATION OF LESIONS

The great majority of tuberculous lesions developing in the alimentary tract are located in the *terminal ileum* and *cecum*. Predilection for this site may possibly be related to certain anatomic and physiologic characteristics of these portions of the alimentary tract. Rokitansky[14] and others have emphasized that the first tubercles developing in the alimentary tract usually are in the *lymphoid tissue*. Lymphoid tissue is particularly abundant in the terminal ileum and cecum. The progress of the intestinal contents is appreciably and comparatively slower in the ileocecal region. Thus the longer exposure of bacilli-laden intestinal contents in areas rich in lymphoid tissue may help to explain the comparatively greater frequency of tuberculosis in the ileocecal region than elsewhere. In clinical and roentgenologic studies it is of course important to recognize that the ileocecal region is the site of predilection. Frequent fluoroscopic and roentgenologic observations directed toward this part of the alimentary tract aid greatly in the usually rather difficult diagnosis of intestinal tuberculosis.

In 230 instances of fatal tuberculosis, Goldberg and coworkers[8] at autopsy found the following percentage incidence of tuberculosis in different parts of the alimentary tract: tongue 0.6, stomach 0.6, duodenum 3.8, jejunum 21.2, ileum 83.2, cecum 87, appendix 39.1, colon 71.7 and sigmoid and rectum 16.3 per cent.

I have seen three patients with subacute tuberculous appendicitis during the past year, all of whom were operated on with good recovery. Scattered tubercles were present on the peritoneum of other abdominal viscera in all three cases. Some tuberculous involvement of the appendix is not uncommonly found in our autopsy cases.

Serial sections of intestinal lesions corroborate the opinion that tubercle bacilli may pass through the mucous membrane apparently without producing definite pathologic changes.

then become localized in the submucosal lymphoid tissue and produce *tubercles* (Gardner[7] and Rokitansky[14]). If the disease progresses, tubercles coalesce, caseate and extend to and perforate the mucosa and ulceration results. Apparently, secondary pyogenic infection of the ulcer quickly develops with characteristic changes in the inflammatory reaction of the surrounding tissue. Should the disease continue to progress, the ulceration may become deeper, more extensive and long tracts may be found in the submucosa.

COMPLICATIONS AND SEQUELAE

Lymphatic metastases may result in the development of localized or generalized *peritonitis* or *mesenteric lymphadenitis*. Rarely, perforation of the wall of the intestine with resulting generalized peritonitis may occur. Usually, however, if perforation occurs, adhesions tend to localize the peritonitis. *Fecal abscesses* occasionally develop after intestinal perforation.

In chronic tuberculous enterocolitis, the intestinal wall may become greatly thickened as a result of hyperplastic changes and adhesive peritonitis. Occasionally deep circular ulcers heal, leaving extensive scarring and cicatrix with *stenosis*. The intestines may become markedly dilated proximal to the stenosis. Such sequelae undoubtedly explain certain gastro-intestinal symptoms and abdominal findings in patients with arrested pulmonary and intestinal tuberculosis. A patient was recently seen who had had both active pulmonary and intestinal tuberculosis eleven or twelve years previously. His pulmonary tuberculosis had been arrested for several years but he continued to have vague intestinal symptoms. Proctoscopic examination revealed considerable stricture in the sigmoid region without evidence of active disease or ulceration. This finding was thought to be due probably to healed tuberculosis resulting in partial stenosis of the sigmoid.

HEALING

Prior to the work of Brown and Sampson,[5] and Gardner,[7] most clinicians regarded intestinal tuberculosis as a fatal complication of pulmonary tuberculosis. In a group of eighty-

two Saranac patients dead of pulmonary tuberculosis and found at autopsy to have intestinal tuberculosis, Gardner[7] noted that thirty-eight or 46.3 per cent had some evidence of healing, and sixteen or 19.5 per cent had "complete healing of all intestinal lesions." Many of these patients had received heliotherapy and a special bland and high vitamin C and D diet. Smith[15] and McConkey,[12] Gardner[7] and others believe that such diets augment the natural tendency to healing in many patients. This is also the writer's impression especially in patients showing a natural tendency to heal the pulmonary disease. Healing of the intestinal lesions apparently depends largely upon the patient's natural and acquired resistance, the extent and severity of the involvement and the ability of the patient and physician to control the pulmonary disease. Such control shuts off the source supply of bacilli to the intestines.

SYMPTOMATOLOGY AND DIAGNOSIS

Patients having considerable tuberculous enterocolitis may have no recognizable gastro-intestinal symptoms. Often, when symptoms are present, they are vague or indefinite and not likely to attract the attention of patient or physician. However, patients having pulmonary tuberculosis and any of the following symptoms should be suspected of having intestinal tuberculosis: recurring or persistent *anorexia*, vague *indigestion*, slight or severe *colicky pain* especially in the lower abdomen, often appearing or becoming worse after eating, *constipation* or *diarrhea*, or alternating constipation and diarrhea, slight or occasionally severe *nausea* with or without vomiting, *inability to gain weight* despite improvement of the pulmonary disease, rapid and undue *loss of weight*, and an irregular or swinging *temperature* curve which is occasionally higher in the forenoon. The type and severity of the gastro-intestinal symptoms are usually related to the severity and location of the enterocolitis and accompanying complications, such as localized or generalized peritonitis, subacute or acute tuberculous appendicitis, perforation or stenosis of the intestine, or tuberculous mesenteric lymphadenitis.

Physical examination of the abdomen is usually inconclu-

sive. Slight pain, soreness or tenderness on deep palpation may be elicited especially in the right lower quadrant, less often over the lower half of the abdomen. Muscular spasm may be slight or occasionally marked depending upon the presence of an accompanying peritonitis which is not rare in young females, more especially of the colored race.

Roentgenologic Studies

Since the symptoms and physical findings are inconclusive, and usually insufficient to make a definite diagnosis, patients having pulmonary tuberculosis and symptoms or findings suggestive of gastro-intestinal tuberculosis should have careful roentgenologic studies. Such studies may be carried out as recommended by Brown and Sampson[5] or Boles and Gershon-Cohen[4] and others. The latter favor the use of the *double contrast barium enema* in preference to the barium meal advocated by Brown and Sampson.[5] They claim that the double contrast enema is not only a less expensive procedure, but also less troublesome for the patient. In addition to revealing evidence of segmental irritability and hypermotility, the double contrast enema may provide accurate demonstration of the actual morbid anatomic changes of a diseased segment of the bowel in many cases. Irregular mottling of the barium coating the diseased mucosal lining is often noted in cases with minimal lesions and more definite irregularities of the mucosal lining may be present in cases with more advanced lesions.

If a diagnostic *barium meal* has been given, fluoroscopic and radiographic observations should begin no later than the fourth or fifth hour after ingestion of the meal and probably should be continued at every half, or hour intervals, after the sixth or seventh hour, depending upon the findings, until the tenth or twelfth hour. Segmental irritability or generalized hypermotility evidenced by complete emptying of the colon in twenty-four hours, or failure of certain portions of the intestine, especially the ileocecal region, to retain the barium for a normal period of time, the presence of spastic filling defects on repeated observations, and gastric retention, are the important positive findings on roentgenologic study fol-

lowing a barium meal. If the fluoroscopic and radiographic findings are inconclusive, as they not infrequently are, a double contrast barium enema should be given at some later date.

Pseudo filling defects may lead to false positive diagnoses and for this reason *frequent* fluoroscopic observations, especially between the sixth and tenth or twelfth hours, should be made with especial attention directed toward the ileocecal region. Evidence of localized irritability and general hypermotility and constant filling defects are not pathognomonic of tuberculous enterocolitis. Ulcerative enterocolitis due to other etiologic factors may cause similar abnormal intestinal function, and these conditions must be borne in mind in order to make a proper differential diagnosis. Conversely, patients with an ulcerative enterocolitis of unknown or obscure etiology should always have a chest roentgenogram to rule out the possibility of the intestinal condition being secondary to pulmonary tuberculosis. However, such findings in patients suffering from active pulmonary tuberculosis usually warrant a diagnosis of intestinal tuberculosis.

TREATMENT

Prevention.—The prevention of gastro-intestinal tuberculosis should not be considered entirely theoretical. The early diagnosis of pulmonary tuberculosis and its early control either by proper general management in a hospital or sanatorium including absolute bed rest, and should this fail, the early use of collapse therapy when not contraindicated, a high caloric and high vitamin diet, combined with teaching the patient, especially young women, the dangers of swallowing particles of bacilli-laden sputum, and meticulous mouth hygiene, should materially aid in preventing large and repeated doses of bacilli being swallowed and should, therefore, reduce the likelihood of the patient developing serious clinical tuberculosis of the alimentary tract.

Hygienic and Dietary Measures; Heliotherapy.—There is no known specific medication for the treatment of intestinal tuberculosis. The usual hygienic sanatorium and hospital treatment, including prolonged bed rest, the use of a bland

noncellulose diet, as advised by Alvarez, large doses of vitamins, parenterally if necessary, especially vitamin C, iron and concentrated liver extract by mouth if secondary anemia is present, are all helpful. Natural or artificial general heliotherapy in gradually increasing doses may be of value if the patient is not acutely ill or having hemoptyses.

Symptomatic Measures.—Certain medications may be necessary and helpful in the control of such symptoms as constipation, diarrhea and severe colicky pain. Constipation should be controlled since it may be an important factor in the development or aggravation of the existing intestinal lesions. The control of diarrhea is important in order to prevent dehydration and demineralization and marked emaciation. The intravenous use of 10 cc. of 5 or 10 per cent calcium chloride solution is useful for this purpose. Certain opium derivatives and bismuth may also be useful in less severe attacks of diarrhea and abdominal pain. Calcium gluconate and calcium subgallate are advocated by some. The surgical removal of a tuberculous appendix, a fallopian tube, or the most involved portion of the intestine may be occasionally necessary.

Early Control of the Pulmonary Disease.—Since the pulmonary disease is practically always the source of supply of bacilli that initiate tuberculous enterocolitis, the shutting off of this supply and the control of the pulmonary disease with the usual consequent improvement in the patient's natural resistance to tuberculosis is the most important counterattack against intestinal foci. Tuberculosis is a systemic disease. However, the control of the enemy's citadel of strength—the pulmonary foci—usually means the control and eradication of his secondary outpost—the intestinal foci. This can be more successfully accomplished by earlier diagnosis of the pulmonary and intestinal disease, earlier adequate treatment, especially the earlier use of collapse therapy if it is not definitely contraindicated. When prompt and adequate treatment is directed to both the citadel of strength and the secondary intestinal outpost, the prognosis in these patients frequently becomes much less grave than it was considered to be ten or fifteen years ago. Today, tuberculosis of the ali-

mentary tract is no longer considered the "mortal symptom" of Hippocrates.[10] The best prophylactic or active treatment of this alimentary complication is early control of the pulmonary disease.

BIBLIOGRAPHY

1. Alvarez, W. C.: Treatment of Nervous Indigestion. J.A.M.A., 89: 440–445. 1927.
2. Aretaeus: Quoted by Brown and Sampson, Intestinal Tuberculosis. Lea and Febiger, Philadelphia, 1930.
3. Bayle, G. L.: Recherches sur la phthisie pulmonaire, 1810.
4. Boles, Russell S. and Gershon-Cohen, Jacob: Intestinal Tuberculosis. J.A.M.A., 103: 1841–1844 (Dec.) 1934.
5. Brown, Lawrason and Sampson, H. L.: Intestinal Tuberculosis, Diagnosis and Treatment. Lea & Febiger. Philadelphia, 1930.
6. Cullen, James H.: Intestinal Tuberculosis. Quart. Bull. Sea View Hospital, Vol. V, No. 2, January, 1940.
7. Gardner, L. U.: Pathological Anatomy of Intestinal Tuberculosis, Chapter VI, in Intestinal Tuberculosis, L. Brown and H. L. Sampson.
8. Goldberg, Benjamin: Clinical Tuberculosis. F. A. Davis Co. Philadelphia, 1941, Vol. 2.
9. Hardt, Leo L., Weissman. Morris. Coulter, John S. and Henrichsen. Karl J.: Treatment of Gastro-intestinal Tuberculosis. J.A.M.A., 112: 691–696 (Feb.) 1939.
10. Hippocrates: Quoted by Brown and Sampson.
11. Louis, P.-C.-A.: Recherches anatomiques, pathologiques et thérapeutiques sur la phthisie, 2. éd., Paris, Baillière, 1843.
12. McConkey, M.: The Treatment of Intestinal Tuberculosis with Cod-liver Oil and Tomato Juice. Trans. Nat. Tuberc. Assn., 25: 105–113, 1929.
13. Morton. Richard: Phthisiologia. 1694.
14. Rokitansky, Carl: Manual of Pathological Anatomy, v. 2, trans. by Edward Sieveking, London, Sydenham Soc., 1849.
15. Smith, David T.: Quoted by L. Brown and H. L. Sampson.

THE SWEDISH HOSPITAL

OFFICE TREATMENT OF HEMORRHOIDS

FRANK C. YEOMANS, M.D., F.A.C.S.*

PRELIMINARY to a discussion of the treatment of hemorrhoids, a brief review of certain related anatomical features is in order.
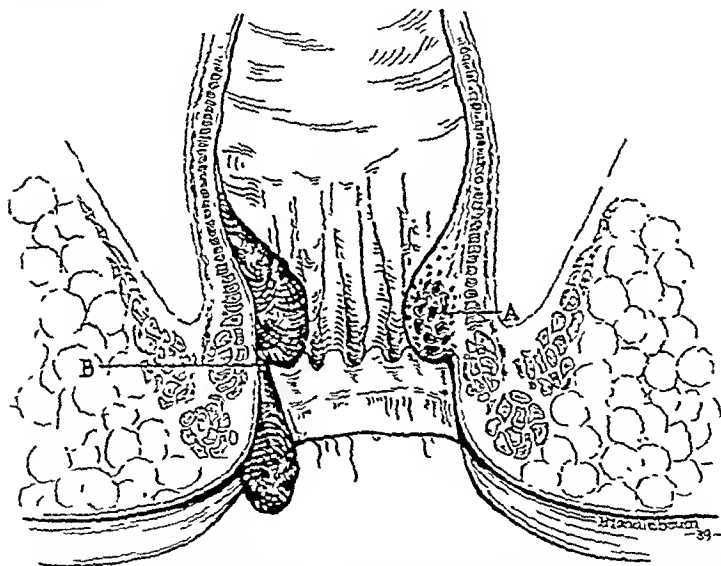
Fig. 141.—Cross section of anorectum (diagrammatic). *A*, Internal hemorrhoids; *B*, mixed or combined external hemorrhoids. (Author's book on "Sclerosing Therapy," Wm. Wood & Co., Baltimore, Md.)

Absorption of the anorectal membrane toward the end of the second month of embryonal life leaves a permanent annular zone of demarcation, the *pectinate line*, which is a clinical landmark of paramount importance. It marks the upper limit of the modified skin lining the anal canal, having

* Professor of Proctology, New York Polyclinic Medical School and Hospital.

squamous epithelium, and the mucosa of the rectum proper above with its columnar epithelium. The anal skin has a rather poor blood supply but is rich in sensitive nerve endings, while the rectal mucosa is freely movable and is not sensitive. Hence, minor surgical procedures can be carried out on the rectal mucosa without pain. The *lymphatics* below the pectinate line drain through the perineum to the superficial inguinal nodes, while those above it drain upward. It seems probable that the rich supply of lymphatics in the submucosa of the rectum is an important factor in taking care of chemical agents injected in the submucosa.

Hemorrhoids are classified as external, internal and mixed or combined interno-external hemorrhoids (Fig. 141).

EXTERNAL HEMORRHOIDS

External hemorrhoids are of only slight clinical significance unless they become thrombotic, usually as a result of physical strain. The term "thrombotic" is largely a misnomer, for what actually happens is the rupture of a vein and clot formation in the subcutaneous connective tissue at the anal verge. If the clot is small it may be absorbed or organize into fibrous tissue, following the application of compresses of 25 per cent solution of magnesium sulfate or lead and opium lotion. When the clot is large and painful, the best procedure is to infiltrate the overlying skin with 2 per cent novocain solution, excise an ellipse, evacuate all blood clots and apply compression with adhesive tape over a small pad of sterile gauze (Figs. 142 and 143). Complete healing *per primam* usually occurs in five days. Then the rectum should be examined for internal hemorrhoids, since frequently external hemorrhoids are evidence of internal hemorrhoids with which they are connected by small venules running beneath the lining of the anal canal.

INTERNAL HEMORRHOIDS

Internal hemorrhoids are varicose swellings of radicles of the superior hemorrhoidal vein. They are situated in the submucosa of the rectum just above the pectinate line, commonly in the left posterior quadrant and the right anterior

and posterior quadrants. These are the *primary* internal hemorrhoids but *secondary* hemorrhoids to the number of five may develop. The most usual secondaries are one posterior and, in women, one anterior just to the right of the midline.

The mucosa overlying each internal hemorrhoid is arranged in a longitudinal fold (column of Morgagni). It is a
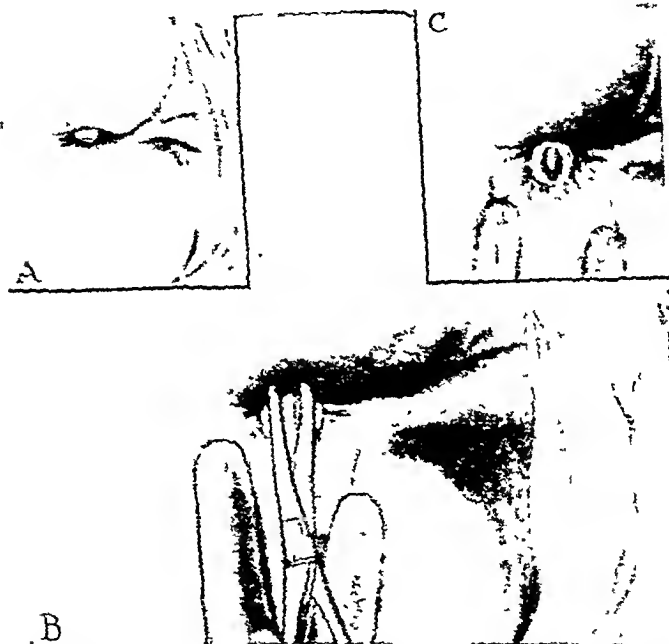
Fig. 142.—External thrombotic hemorrhoids. *A*, The thrombosed hemorrhoids, *B*, method of excising an ellipse of overlying skin by a single clip of scissors curved on the flat; *C*, clot protruding through the incision. (Author's book on 'Proctology," D. Appleton-Century Co.)

deep beef color or may be granular, or the site of superficial erosions or abrasions, due to infection or trauma by hard feces.

The vessels implicated are a conglomerate mass of dilated venules and unchanged arterioles in a stroma of connective tissue. Fibrous tissue replacement of its elastic and muscular coats produces a dilated vein with a thin fibrous wall which

is prone to rupture as a result of fecal or instrumental trauma. Chronic congestion, infection from the anal crypts or through the mucosa, or thrombosis in, or extravasation of blood from, the diseased veins causes a chronic productive inflammation of the interstitial connective tissue. Contraction of this tissue tends to obliterate the venules. Spontaneous cure results or the hemorrhoid becomes a fibrous nodule—"white hemorrhoid." Examination should detect these conditions because they bar treatment by injection.

Fig. 143.—External thrombotic hemorrhoids. Method of applying long strips of adhesive to obtain pressure and prevent bleeding after operation. (Author's book on "Proctology," D. Appleton-Century Co.)

The mucosa of the hemorrhoidal zone is freely movable over the muscular coat to which it is weakly attached by the intervening submucosa. If the sphincter muscles are relaxed, the hemorrhoids tend to prolapse; but pathologic conditions at the pectinate line, such as cryptitis and fissure, cause irritation and spasm of the sphincter which usually prevents protrusion. If hemorrhoids prolapse through spasmodic sphincters they should be reduced at once. Otherwise they become strangulated and irreducible. Ensuing venous thrombosis is

then frequently followed by pressure necrosis of the mucosa and rarely by infection and abscess formation.

Symptoms and Signs

The symptoms and signs of internal hemorrhoids closely parallel the pathologic changes within the hemorrhoids themselves and the degree of prolapse. The leading symptoms are bleeding and prolapse.

Clinically, uncomplicated internal hemorrhoids are classified, according to their degree of development, as:

Primary or *first stage*, characterized by the passage of bright red blood with the stool, but without prolapse.

Intermediate or *second stage*, marked by prolapse at defecation which is reduced spontaneously, and only slight bleeding because of interstitial fibrosis within the hemorrhoid.

Final or *third stage* in which there is little or no bleeding, but manual reduction is required to replace the prolapse which recurs on slight exertion and, if the sphincters are relaxed, remains continuously protruded. Excess mucus from the mucosa, exposed to friction, and discharge from the bowel irritate the perianal skin.

Diagnosis

Before beginning any treatment of hemorrhoids it is essential to rule out any other lesions that may cause bleeding. The diagnosis of internal hemorrhoids is made by *inspection* and *palpation*. With the patient in the left lateral position and the buttocks retracted, internal hemorrhoids may be protruded if the sphincters are relaxed, but if the sphincters are spasmodic they cannot be seen. By digital palpation, folds of mucosa may be felt, but only those hemorrhoids can be recognized which are thrombosed or fibrotic. Direct inspection of the entire pile-bearing zone through a fenestrated or tubular anoscope is next in order. With good illumination, the examiner recognizes the type of hemorrhoids present and inspects the pectinate line for signs of infection, such as cryptitis, and the anal canal for fissure.

Proctosigmoidoscopy should never be omitted. The majority of colonic adenomata and over 70 per cent of cancers of

the large bowel are situated in the rectum and rectosigmoid.
Yet, reliable statistics show that more than 15 per cent of the
latter were treated for hemorrhoids within the year prior to
the correct diagnosis of cancer. If indicated, a roentgen study
of the gastro-intestinal tract should be made.

Treatment of Internal Hemorrhoids

Internal hemorrhoids may be treated by operation, by elec-
tricity or by injection.

Surgery.—Since operative treatment by ligature, the clamp
and cautery, and excision and suture effect a cure in 95 per
cent of cases, I advise surgery in all suitable cases. Because of its
simplicity and the good results obtained, the ligature method
is commonly used. As this article deals with office treat-
ment only, the technic of these operations is omitted here
but it is described in detail elsewhere.[1]

Electricity.—Galvanism, electrodesiccation and surgical
diathermy (electrocoagulation) have a limited vogue as office
procedures. Special technical training and the cumbersome
apparatus required together with the uncertain control of
tissue penetration and destruction render electrical methods
of little practical value.

Injection Treatment

INDICATIONS AND CONTRAINDICATIONS.—Since treatment by
injection was first employed empirically in 1871, it has
evolved into a sound scientific procedure. *It is indicated only
for uncomplicated internal hemorrhoids.* When the internal
hemorrhoids are complicated by sphincter spasm, papillitis,
cryptitis, fissure, fistula or thrombotic external hemorrhoids,
and if there is prolapse not reduced spontaneously, the best
procedure is radical surgery whereby at one step the hemor-
rhoids are removed and the complications corrected.

Special indications for injection treatment are found in pa-
tients who are poor surgical risks because of diabetes, pul-
monary tuberculosis, cardiorenal-vascular disease, old age,
early pregnancy, purpura or hemophilia, or anemia secondary
to bleeding from internal hemorrhoids in which the hemo-
globin may be as low as 30 per cent.

SOLUTIONS.—The two chemical agents which time and experience have proved to be satisfactory are phenol and quinine and urea hydrochloride. As a result of study and experience, the optimum strength of solutions to be used and a satisfactory technic for their employment have evolved. Nevertheless, no one should practice this form of therapy until he has obtained adequate practical instruction from a surgeon skilled in its technic.

Phenol, the original chemical agent used for injection, is mildly anesthetic and strongly antiseptic. The desideratum is an aseptic inflammatory reaction, obtained by a 10 per cent to 20 per cent solution in equal parts of glycerin and water, or 5 per cent in a *vegetable* oil, preferably oil of sweet almond. Animal oils are absorbed too quickly and mineral oil is not absorbed but remains as a foreign body.

Quinine and urea hydrochloride was introduced by Terrell in 1913, in a 5 per cent solution in distilled water. As a solution of tablets in water is only mildly antiseptic and not stable, only a freshly prepared solution should be used, or, better, sterile ampules. Idiosyncrasy to quinine bars the use of quinine and urea in susceptible persons.

The aseptic inflammatory reaction following the injection of hemorrhoids results in a interstitial fibrosis and intravascular clotting, with symptomatic relief.

TECHNIC.—The patient, with rectum empty, is placed in the left lateral position on a firm table. Illumination from a head light or head mirror is satisfactory. An anoscope of the open-end type or the fenestrated Brinkerhoff is inserted its full length, the obturator removed and the instrument withdrawn to the pectinate line, thus exposing all the hemorrhoids when the tubular speculum is used. When using the Brinkerhoff, the speculum is adjusted so that, as the slide is withdrawn to the dentate line, the hemorrhoid to be treated protrudes into the slot.

Depending upon the size of the hemorrhoid, from 3 to 10 minims of the 10 per cent solution of phenol are injected very slowly into the center of the hemorrhoid and well above the dentate line, with a needle of 25 gauge attached to a tuberculin syringe (Fig. 144). Any oozing of blood or leak-

age of fluid from the point of puncture should be checked by pressure with a pledget of cotton before the speculum is removed.

Some surgeons inject two or more hemorrhoids at the same sitting but I usually treat only one at a sitting, beginning with the largest and the most actively bleeding. From four to eight treatments are effective in an average case. Unless the pile is completely shrunken at the end of three weeks, it is injected again.
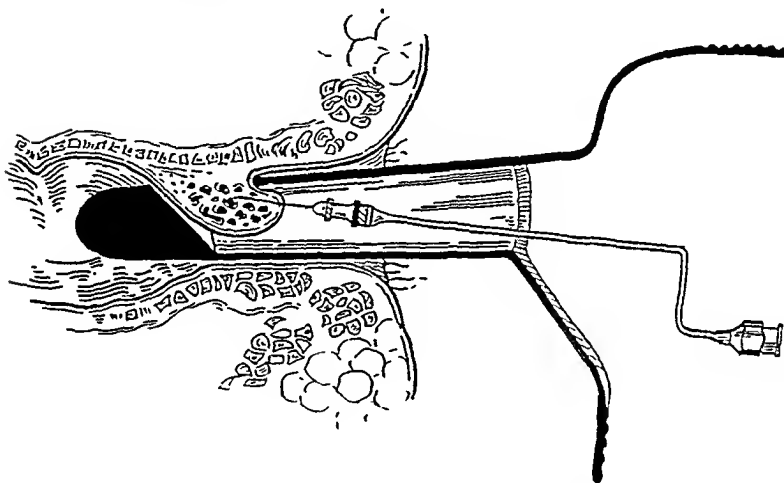
Fig. 144.—Technic of injection into the center of an internal hemorrhoid through the Brinkerhoff speculum. (Author's book on "Sclerosing Therapy," Wm. Wood & Co., Baltimore.)

From 1.0 to 1.5 cc. of the quinine and urea solution are injected into the center of each hemorrhoid to moderate distention.

Injection of *phenol in oil* is especially indicated for prolapsing internal hemorrhoids or when the rectal mucosa above is relaxed and redundant. With a 10-cc. Luer-Lok syringe armed with an extension needle of 20 gauge and filled with the oil solution, the mucosa at the upper pole of the hemorrhoid is punctured and from 2 to 6 cc. are deposited slowly in the submucosa (Fig. 145). Slight blanching of the mucosa indicates that the correct amount has been injected.

The objective of phenol in oil injections is to excite an aseptic productive inflammatory reaction in the submucosa. The resulting fibrosis, in its contraction, tends to draw up and fix the mucosa to the musculature, and to obliterate the adjacent hemorrhoid. If the latter objective is not obtained at the end of two weeks, from 3 to 10 minims of the 10 per cent aqueous solution of phenol are injected directly into the center of the hemorrhoid.

An interval of five to seven days between treatments is desirable. After injection the patient should refrain from
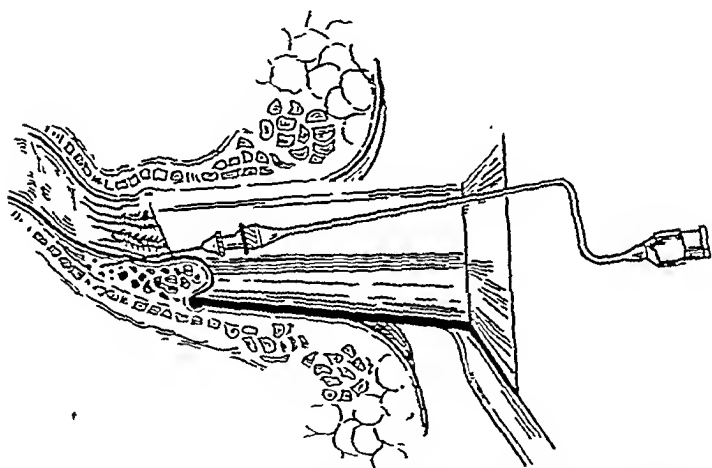
Fig. 145.—Technic of submucous injection through a tubular speculum. (Author's book on "Sclerosing Therapy," Wm. Wood & Co., Baltimore.)

severe physical exertion until the next day, but may keep business and social engagements. Regular diet is allowed and daily bowel evacuations are advised.

COMPLICATIONS.—Complications are relatively rare and are usually due to faulty technic or injecting unsuitable cases. If too much solution is injected or if it is deposited in the mucosa, a mucosal *slough* may result, with more or less bleeding. As injections are made in a nonsensitive zone, treatments should be painless. Occurrence of pain during injection suggests that puncture has been made so near the pectinate line that some of the solution has infiltrated beneath the sensitive

lining of the anal canal. Ulcer of the canal and thrombotic external hemorrhoids may ensue.

Infection, followed by abscess, septicemia, abscess of the liver and stricture are other complications that have been reported, but they have not occurred in my practice.

Recurrence within one to five years is to be expected in about 20 per cent of cases, but frequently patients are so well satisfied that they have another course of injections.

CONCLUSIONS.—After several years of personal experience in a large number of cases, with no deaths or serious complications, I feel that treatment by injection fulfills the requirements of a satisfactory ambulatory method of therapy for suitable cases of *uncomplicated internal hemorrhoids* because (1) no anesthesia is required, (2) it is painless, (3) there is no detention from business, (4) there is prompt symptomatic relief which is permanent in approximately 80 per cent of cases, and (5) it is economical in time and hospital charges for the patient.

BIBLIOGRAPHY

1. Yeomans, F. C.: Treatise on Proctology, 2nd Ed. D. Appleton-Century Co., New York, 1936.
2. Yeomans, F. C.: Sclerosing Therapy. Wm. Wood & Co., Baltimore, 1939.

DYSFUNCTION OF THE LIVER

Some Common Clinical Varieties*

JOHN RUSSELL TWISS, M.D., F.A.C.P.†

THE term "dysfunction of the liver" means impaired function of the liver. There are many functions of the liver and no one test is adequate to indicate its general functional capacity. It therefore seems desirable to approach the subject from a clinical viewpoint. Since the present discussion is concerned primarily with the practical management of some of the more common types of hepatic dysfunction, a clinical classification would seem best for purposes of discussion. This is particularly true because the vast majority of clinicians have no facilities for the numerous laboratory tests which have been devised to determine impaired liver function. For this reason, only those laboratory tests will be considered which are relatively easy to perform and which give findings which can be interpreted without benefit of great laboratory experience.

In this discussion the term *acute, nonobstructive dysfunction* of the liver will include the type characterized by jaundice, relatively gradual in onset, unaccompanied by acute pain. *Acute obstructive dysfunction* includes those cases of impaired liver function indicated by the relatively rapid onset of severe jaundice, usually preceded by acute pain. In this group are included cases of extrahepatic obstruction, usually organic in nature, requiring surgical intervention. In the *chronic dysfunction* group are included those patients having chronic disease of the liver, usually intrahepatic in type, in which medical therapy is indicated.

*From the Biliary Tract Clinic, Department of Medicine, New York Post Graduate Hospital.

†Assistant Clinical Professor of Medicine, New York Post Graduate Medical School, Columbia University; Assistant Attending Physician, New York Post Graduate Hospital.

ACUTE NONOBSTRUCTIVE DYSFUNCTION

In acute nonobstructive liver dysfunction I shall include those cases generally assumed to be due to hepatitis, either catarrhal, infectious, or toxic in origin. The history is usually brief; the gradual onset of jaundice, not associated with severe abdominal pain, is reported in most cases within the period of a few days. There are several reasons for this unusual promptness in seeking medical attention. The first is the startling appearance of the patient, his unaccustomed "jaundiced eye" and unattractive skin immediately suggests to the untutored eye a serious illness. In addition, the distressing symptoms of anorexia, nausea, vomiting and epigastric discomfort following the intake of food urgently impels the average patient to visit the doctor.

Diagnosis

In taking the *history* of these patients we must keep in mind the fact that the majority of patients with jaundice, ill enough to be admitted to the hospital, have gallstones. While most of these cases have a history of chronic recurrent indigestion and acute attacks of abdominal pain preceding the onset of the jaundice, the possibility of a so-called "silent stone" must always be remembered. A differential point of some practical value is the *age* of the patient. Noncalculous jaundice is common under the age of forty years, less common after the age of forty. In the age group over forty, the incidence of carcinoma of the biliary tract or pancreas, pancreatitis and cirrhosis of the liver is relatively high.

The history of the jaundiced patient cannot with safety be limited to the investigation of the digestive symptoms. We must consider the patient himself, the age group and sex. In gallbladder disease we have found that females may predominate over males as much as 20 to 1, whereas almost the reverse holds true in patients with liver disease. The predominance of males having liver disease is far less striking, nevertheless the fact remains that males constitute the majority of patients with proved liver disease.

Occupational hazards occupy a definite position in some cases of jaundice; *toxic hepatitis* may result from exposure to

certain chemicals. As examples should be mentioned the cleaner employing carbon tetrachloride, the airplane maker exposed to the fumes of trinitrotoluene or tetrachlorethane, and the match maker dealing with phosphorus. Inquiry should also be made about drugs or injections taken. Toxic hepatitis may also result from oral or intravenous medication. Probably the most common offenders are cinchophen, atophan, mercury, arsenic, salvarsan and the sulfonamides. Anesthetics as chloroform or avertin may also cause liver damage.

While *catarrhal jaundice* is usually classified as an acute infectious hepatitis, certain evidence suggests that in some cases an acute gastro-enteritis (with a duodenitis) may be the actual precipitating cause of the jaundice. The common history of preceding exposure to cold or wet weather and getting chilled is well known. With this, frequently, come anorexia, nausea and vomiting, sometimes with diarrhea.

Similar symptoms are found in the so-called *epidemic type* of jaundice, where a number of closely-associated people may be affected more or less simultaneously. The etiologic factor in these cases would seem to be some type of infection probably transmitted through the medium of food or water. Gastric analysis in most of these cases will show gastric hyperacidity, while cultures of duodenal bile are almost invariably sterile. In passing, mention should be made of the jaundice associated with acute infectious systemic conditions such as pneumonia, typhoid fever, and various tropical fevers.

Laboratory tests are of some value in differentiating between intrahepatic and extrahepatic types of jaundice if done early in the course of the jaundice rather than after a period of weeks. Among those tests which apparently reliably indicate liver damage are a positive galactose tolerance test, a positive urobilinogen test, an elevated serum bilirubin determination and a positive Hanger cephalin flocculation test. The absence of an obstructive lesion of the common bile duct is suggested by a normal phosphatase reading and the presence of adequate amounts of bile in the specimens obtained by the duodenal tube. If no bile is obtained the position of the tube must be checked by fluoroscopic inspection.

Treatment

Treatment in this group of cases is essentially the same in all. Removal of the source of the disability is occasionally possible, by stopping medication or injections. *Bed rest* is distinctly beneficial in most cases, especially in the early stages. Hospital treatment will aid in the avoidance of detrimental conditions such as drastic temperature changes, exhaustion and indiscretions in regard to eating and drinking.

DIET.—Dietary management is of the utmost importance. A bland diet is advisable; in the more severe cases associated with nausea and vomiting, a fluid diet may be necessary. In these cases fruit juices, tea and toast may be the only substances tolerated; these should be given every hour or two, only in small amounts. A high caloric diet should be given as soon as it is tolerated, using as far as possible intermediate feedings. These have a threefold value; they build up the glycogen reserve of the liver, maintain nutrition and aid in combating biliary stasis and consequent liver damage by means of promoting the bile flow which occurs in response to food stimulation.

The type of foods given should receive the detailed attention of the doctor. Emphasis must be placed upon the carbohydrate intake; 400 to 500 gm. of carbohydrate daily is not too much. Feedings should be given at intervals of four hours, interspersed with intermediate feedings of milk, tea, or fruit juice. To these should be added cane sugar; dextrose or lactose in 1- to 2-dram doses may be substituted if sugar is not well tolerated. Proteins in adequate amounts are necessary, preference being given to simple proteins such as are found in chicken, roast lamb, lamb chops, lean fish, cottage cheese, peas, beans and gelatin. The total amount of protein should be 80 to 100 gm. Fats should be strictly limited because of the intolerance for fats and oils which occurs in almost all jaundiced patients. In general, the patient should avoid all oils, nuts, salad dressings, thickened gravies, condiments, spices, pickled, smoked and salted foods, inner organs, salads, raw vegetables and raw fruits.

DUODENAL DRAINAGE.—Among other therapeutic measures of value is duodenal drainage. While there is no question that

this procedure has limited therapeutic value in gallbladder disease, there is nothing which gives more striking results in the treatment of the patient with a severe case of catarrhal, toxic or infectious jaundice. The rationale of this treatment is physiologically sound in that it relieves the biliary stasis occasioned by lack of food; the continuous flow of bile over a period of hours frequently relieves in a striking way even the engorgement of the liver and the tenderness over the liver region. There is invariably marked symptomatic relief of the anorexia, nausea and vomiting following duodenal drainage.

MEDICATION.—Medication in these cases is of limited value. So-called biliary tract antiseptics have consistently proved useless. *Saline laxatives*, however, are indicated, the most satisfactory being sodium phosphate, sodium sulfate and magnesium sulfate. A mixture of equal parts of these three substances may be substituted for any independently. The dosage in either case is a dram, preferably in a full glass of warm water, taken before breakfast or before each meal.

Probably one of the most useful medications consists of the use of *antacids* after meals, especially in patients having gastric hyperacidity as shown by the gastric analysis. My own preference is for a mixture of 2 parts of calcined magnesia and 1 part of calcium carbonate, a dram being taken with a half glass of water after meals. The laxative effect of the calcined magnesia is especially useful when there is any tendency to constipation. The addition of an equal part of bismuth subcarbonate has good effects in severe cases of gastritis. The addition of *vitamins* is also indicated, a capsule of mixed A. B. C. D vitamins being taken twice daily, after breakfast and dinner. Thiamine chloride in doses of 5 to 10 mg. daily has also seemed beneficial. In patients able to tolerate brewers' yeast, large doses are also indicated.

ACUTE OBSTRUCTIVE DYSFUNCTION

Clinically, acute obstructive liver dysfunction is characterized by abrupt and progressive jaundice, usually coming on a variable period of time after the onset of an acute attack of biliary colic. The time which elapses between the

Treatment

Treatment in this group of cases is essentially the same in all. Removal of the source of the disability is occasionally possible, by stopping medication or injections. *Bed rest* is distinctly beneficial in most cases, especially in the early stages. Hospital treatment will aid in the avoidance of detrimental conditions such as drastic temperature changes, exhaustion and indiscretions in regard to eating and drinking.

DIET.—Dietary management is of the utmost importance. A bland diet is advisable; in the more severe cases associated with nausea and vomiting, a fluid diet may be necessary. In these cases fruit juices, tea and toast may be the only substances tolerated; these should be given every hour or two, only in small amounts. A high caloric diet should be given as soon as it is tolerated, using as far as possible intermediate feedings. These have a threefold value; they build up the glycogen reserve of the liver, maintain nutrition and aid in combating biliary stasis and consequent liver damage by means of promoting the bile flow which occurs in response to food stimulation.

The type of foods given should receive the detailed attention of the doctor. Emphasis must be placed upon the carbohydrate intake; 400 to 500 gm. of carbohydrate daily is not too much. Feedings should be given at intervals of four hours, interspersed with intermediate feedings of milk, tea, or fruit juice. To these should be added cane sugar; dextrose or lactose in 1- to 2-dram doses may be substituted if sugar is not well tolerated. Proteins in adequate amounts are necessary, preference being given to simple proteins such as are found in chicken, roast lamb, lamb chops, lean fish, cottage cheese, peas, beans and gelatin. The total amount of protein should be 80 to 100 gm. Fats should be strictly limited because of the intolerance for fats and oils which occurs in almost all jaundiced patients. In general, the patient should avoid all oils, nuts, salad dressings, thickened gravies, condiments, spices, pickled, smoked and salted foods, inner organs, salads, raw vegetables and raw fruits.

DUODENAL DRAINAGE.—Among other therapeutic measures of value is duodenal drainage. While there is no question that

tion to the common duct stone causing the jaundice a cystic duct stone with impaired circulation and a gangrenous gallbladder wall. In other words, an acute cholecystitis may have resulted from the mechanical factors of the obstruction. In the aged such a condition may exist coincidentally with findings of a normal temperature, pulse and blood count. Needless to say, findings of this character justify an immediate surgical consultation. An enlarged palpable gallbladder is seldom found, in our experience, except with hydrops or empyema of the gallbladder, unless we are dealing with the "Courvoisier gallbladder" which results from a gradual noncalculous obstruction of the common duct. An enlarged firm liver usually occurs with common duct obstruction.

The immediate necessity in cases of this kind is to determine as quickly as possible whether we are dealing with a case which should be treated medically or surgically. Among the *laboratory tests* which have proved very helpful in the early stages of jaundice is the icterus index test. If repeated every five to seven days, this test gives a more accurate idea of the course of the jaundice and the likelihood of a permanent obstructive lesion. Normal readings are from 4 to 8 units. The serum bilirubin test is also of value in showing variable degrees of liver damage, in readings of over 2 mg. per 100 cc. A negative Hanger cephalin flocculation test, with jaundice, strongly suggests common duct obstruction. An elevation of the serum phosphatase of over 10 units confirms this impression. It is here necessary to stress, however, that prolonged extrahepatic biliary obstruction will invariably result in liver damage.

In patients having severe jaundice associated with dark urine and clay-colored stools, a complete common duct obstruction is suggested. In these cases there is nothing of greater diagnostic value than the *duodenal tube*. Complete common duct obstruction rarely if ever occurs except as the result of a malignancy. If the duodenal drainage gives no bile the diagnosis of complete common duct obstruction is justified, provided the position of the tube is checked by fluoroscopic examination. Since it is difficult to see duodenal tubes having no metal, especially in the obese, we prefer for purposes of

onset of pain and the onset of the jaundice is largely dependent upon the state of the gallbladder. With a nonfunctioning gallbladder or cystic duct obstruction, the jaundice follows the pain within twenty-four hours; with a functioning gallbladder the jaundice may be delayed three or four days. In any case, the most important consideration is a recognition of the fact that we are here dealing with an organic obstruction of the liver, with the possibility of serious or even fatal consequences if the relief of the obstruction is too long delayed.

The *history* in most cases is that of an individual over the age of forty having jaundice following an attack of pain. It is frequently a female with repeated pregnancies, who has had indigestion for many years. There may be repeated attacks of colic or even jaundice, sometimes with chills, fever, nausea and vomiting. In these cases the prognosis is most serious; surgery should be delayed only long enough for a thorough preparation of the patient for operation. On the other hand, these patients may have had only the usual associated symptoms of indigestion which are belching, distention, discomfort after meals, being "afraid to eat," an intolerance to fats, chronic constipation and loss of weight. Cystic duct or partial common duct obstruction with a stone may furthermore occur with little or no jaundice; the common duct stone may be of the "ball-valve" type. The location of the pain may be of some value in differential diagnosis; the pain in these cases most commonly begins in the epigastrium and tends to radiate to the precordial region. Pruritus usually indicates common duct obstruction.

Diagnosis

Physical examination shows jaundice, possibly fever, with a relatively slow pulse. There are variable findings on abdominal examination. If the symptoms are caused by cholelithiasis, there is frequently an acute localized tenderness of the gallbladder area, frequently with rigidity and sometimes with a palpable mass in the region of the gallbladder. The significance of the acute signs of gallbladder disease must be emphasized, for they indicate that there is probably in addi-

always easy. Another essential test is the complete *blood count.*

Treatment

DIET; CORRECTION OF DEHYDRATION.—The first rule in the treatment of suspected common duct obstruction is to hospitalize the patient. In this way only can the necessary laboratory tests be done and the patient properly prepared for surgery. The diet should be given as outlined for acute liver damage; a glass of fluids with a teaspoonful or a lump of sugar is given every hour if there are no signs of circulatory failure. The correction of dehydration, however, is of fundamental importance; the patient going to operation with a dry tongue is indeed a poor risk. It is furthermore important to keep accurate records of fluid intake and output throughout the period of hospitalization. Intravenous infusions of 1000 cc. of 5 per cent glucose may be given once or twice daily, provided that they are given *slowly* (60 drops a minute) and the patient watched for signs of edema, especially pulmonary. If facilities are available, the electrolyte balance and serum protein determinations as outlined by Scudder are invaluable in the management of the patient who is critically ill.

TRANSFUSIONS.—The presence of a definite anemia is a strong indication for preoperative transfusions, especially in the aged and debilitated. In all patients having a stormy convalescence transfusions are of supportive value and aid in preventing hemorrhage.

VITAMIN K THERAPY.—Hemorrhage has been in the past one cause of a high mortality. At present this dreaded complication has practically disappeared. Among the first tests of the diagnostic work-up should be the prothrombin time. If this is prolonged, immediate treatment with vitamin K or its synthetic equivalents should be started and carried through at least the first week postoperatively. We have used with satisfactory results the 2-methyl-1-4-naphthoquinone and related drugs. Among those used orally with bile salts are *Thyloquinone* (Squibb) and *Proklot* (Lilly), 1 mg. three times daily. For patients coming to operation within a short period of time the hypodermic preparations are probably

orientation the Twiss type which has both a metal bucket and a separate terminal metal ball weight. If on duodenal drainage only blood and duodenal fluid are obtained, after the position of the tube in the duodenum has been confirmed, the diagnosis of malignancy is justified.

Duodenal drainage is a very valuable diagnostic measure, especially in those cases without complete cystic duct obstruction. The character of the bile in containing a sediment of mucus suggests catarrhal cholangitis; pus cells may be found in acute purulent conditions. Crystalline calcium bilirubinate is commonly found with common duct pigment stones, even gross pigmented "sand" may be apparent on gross examination of the bile specimens. Gallbladder stones of cholesterol may be indicated by the presence of cholesterol crystals in the biliary sediment. Specimens of bile obtained under sterile precautions usually give positive cultures, most commonly B. coli, with infectious cholecystitis and with common duct stones.

Although a multitude of other tests have been proposed for the purpose of differentiating between obstructive and intrahepatic types of jaundice, few have been generally accepted. Among those upon which we have come to place reliance, however, are the *cholesterol* and *cholesterol ester determinations* of the blood. It is a well known fact that obstructive types of jaundice are accompanied by elevations in blood cholesterol, which are frequently extreme. The normal figures are from 150 to 220 mg. per 100 cc. of blood. The cholesterol ester determinations should also be done to determine whether the patient is a good operative risk. With severe liver damage there is a marked diminution from the normal ratio of 40 to 50 per cent; with findings of this character strenuous preoperative preparations should precede any operative interference.

Among other routine laboratory tests which should be done in all cases of jaundice is the *blood Wassermann*. Syphilis may cause a hepatitis in the secondary stage, or an enlarged deformed cirrhotic liver in the tertiary stage, when a differential diagnosis as to the cause of the jaundice is not

or swelling of the liver. In this case the pain is most apt to occur in the right upper quadrant. Belching and distention and an intolerance for fats are all common. There is usually an associated furred tongue, bad breath and chronic constipation. Hemorrhage from the mucous membrane of the gastro-intestinal tract is common. Jaundice may occur at any time the intrahepatic or extrahepatic systems create a sufficient resistance to a normal flow of bile. Jaundice is more frequently found after the element of infection has been superimposed upon obstruction. As this recitation of symptoms may suggest, the chronic liver diseases are frequently associated with chronic gastritis and chronic gallbladder disease.

Diagnosis

On *physical examination* these patients are characterized by the appearance of being old beyond their years. The marked malnutrition and emaciation shown by most of them afford a striking contrast to the plump, distended abdomen which most of them possess. With liver obstruction are commonly seen the evidences of collateral circulation on the thorax, varicosities, dilated venules and spider angiomata. Evidence of bleeding may be apparent; probably the most prevalent types are nosebleeds, hematemeses from esophageal varices and intestinal hemorrhages. An icteric pallor is common; actual jaundice occurs usually only in the more severe degrees of obstruction or in the terminal stages of conditions such as cirrhosis. Ascites is common; with this there may be edema of the lower extremities. With symptoms of this character, malignancies must always be suspected.

Abdominal examination in patients of this group presents difficulties, largely because of the presence of fluid in the abdominal cavity. From the viewpoint of the comfort of the patient and the more satisfactory abdominal examination which results, *paracentesis* is frequently a valuable procedure. The character of the fluid obtained by paracentesis is of diagnostic value. The usual fluid of cirrhosis or portal obstruction is clear, amber in color, of specific gravity less than 1.015, with few cells or pathologic elements on the smear of

more satisfactory. *Thyloquinone in oil* (Squibb) may be given intramuscularly in dosage of 1 cc. once or twice daily. *Hydroquinone* (Abbott) may be given in similar dosage subcutaneously or intravenously in urgent cases.

CHRONIC DYSFUNCTION

Chronic liver dysfunction, in contradistinction to the acute forms, is manifested only in the minority of cases by jaundice. In this group are included the patients having liver impairment due to some intrahepatic condition such as cirrhosis or a fatty degenerative liver. There has been a great deal of discussion and controversy as to the causes of these conditions; the matter cannot be considered settled at the present time. Our present evidence seems to indicate, however, that an avitaminosis is one fundamental factor, the most important element of which is vitamin B. Alcohol may play an indirect part in the formation of the cirrhosis, first by causing a nutritional and vitamin deficiency because of the disregard of meals. There is, furthermore, damage to the liver cells in this process, both because of the depletion of the glycogen reserve of the liver and because of the anoxia caused by fatty infiltration and its attendant detrimental factors. An unknown constitutional factor engendering a susceptibility to cirrhosis may also exist, similar to a tendency toward peptic ulcer. Also there should be included in this group those having a biliary cirrhosis secondary to a partial obstruction of the common duct, due to conditions like chronic pancreatitis, chronic cholangitis, duodenitis or common duct stone. Furthermore, the probable detrimental effect of foci of infection should be remembered; on general principles all foci should be treated or removed if possible.

Clinically, these patients give in most cases an indefinite history of indigestion over a relatively long period of time. Anorexia is frequently a symptom of long standing, especially with those addicted to the use of alcohol. Nausea is another common symptom; this is most noticeable in the morning. Distress after eating may be discomfort or actual *pain*. The intensity of the pain, however, seldom approaches that of peptic ulcer unless there is considerable perihepatitis

diagnostic procedures have their advocates, our own experience seems to indicate these are as practical as any. The diagnostic value of the aspirated ascitic fluid has been mentioned. X-ray study of the gastro-intestinal tract should be made to rule out malignancies originating there, with secondary liver metastases. The barium colon enema will give in some cases evidence not obtainable by the gastro-intestinal series. A digital rectal examination, followed if necessary by a proctoscopic examination, supplements the x-ray studies. A complete blood count, urinalysis and Wassermann should, of course, be included in all cases.

Treatment

The treatment of these cases demands much patience and months of time. Ascitic fluid is removed to relieve discomfort. The patient is placed upon a restricted fluid intake of 1500 cc., and salt is prohibited. The *dietary treatment* is similar to that outlined for acute liver dysfunction. *Medication* recently stressed by Patek seems to give best results. Brewers' yeast, from 10 to 20 gm. daily, is given in ice-cold milk flavored with vanilla and nutmeg. Crude liver extract is given intramuscularly, 2 to 3 cc. twice a week. Thiamine chloride is given by mouth, 10 mg. daily. Iron is added if there is an anemia. Vitamins A and D are also useful, Lederle's Vi-Delta Emulsion or mixed vitamin capsules being usually well tolerated. Ammonium chloride by mouth and mercupurin intravenously are necessary in some of the more severe cases. Generally speaking, the carbohydrate and protein intake should be kept at the maximum value compatible with the favorable clinical course of the patient.

With partial obstruction of the common duct, due to the presence of a common duct stone, *surgery* is of course indicated. With conditions such as chronic recurrent pancreatitis, a short-circuiting gallbladder may give great symptomatic relief. In cirrhotic patients with ascites, *not* relieved by careful observance of the regimen outlined, a careful omentopexy as done by Carter may prove decisive in obtaining relief from symptoms.

the centrifuged specimens. Blood in the ascitic fluid suggests malignancy. High counts of polymorphonuclear cells are found with acute infections, high counts of lymphocytes with chronic infections. The presence of mitotic figures justifies the diagnosis of malignancy; the presence of acid-fast bacilli speaks for a tuberculous peritonitis.

Manual palpation following paracentesis is frequently useful in making a differential diagnosis. Neoplasms of the liver are usually secondary to those of the gastro-intestinal tract, a primary mass may be detected in the sigmoid or epigastric region. An enlarged spleen is commonly found with cirrhosis of the portal type. The liver itself in cases of cirrhosis is firm and hard, the size above or below normal. The liver edge may be irregular and "hob-nail" in character; it is not, however, the largely irregular-sized nodular masses of the malignancies or the irregular contracted deformities of the syphilitic. The gallbladder itself is occasionally enlarged and palpable, either with hydrops or empyema, or the Courvoisier gallbladder usually associated with common duct or pancreatic malignancies.

An enlarged spleen produces problems in differential diagnosis. A *familial jaundice* must be suspected in these cases. This is suggested by a history of long-standing recurrent jaundice of a mild degree; other members of the family may have similar symptoms. Laboratory tests are significant in these cases. As outlined by Thompson, the findings consist of an increased fragility of the red cells, an increased reticulocyte count and the presence of spherocytes in the hanging-drop preparation. Another possibility which must be kept in mind, especially in cases of hemorrhage from the mucous membranes, is *Banti's disease*. Here the findings noted for familial jaundice are not present; there are, however, definite findings of cirrhosis as well as splenomegaly. The indications for treatment in these cases are similar; a splenectomy gives good results in most cases.

Laboratory tests seeming to give most accurate results in chronic liver disease include the Hanger flocculation test which becomes positive with liver damage. The hippuric acid and bromsulfalein tests are also good. Although many other

PRIMARY CARCINOMA OF THE LIVER

A Study of Its Diagnostic Features*

ROY UPHAM, M.D., F.A.C.S.†

and

S. D. KLOTZ, M.D.‡

SECONDARY tumors of the liver are estimated to occur twenty to sixty times more frequently than primary tumors in this organ; this is in keeping with Virchow's contention that those organs readily affected by metastasis are rarely the site of primary tumors. although recently there has been an increasing number of reports on primary tumors of the liver. As yet, this syndrome is recognized more frequently in the operating or autopsy room than at the bedside. We are of the opinion that a clinical diagnosis can be obtained ante mortem if a composite of certain clinical features and laboratory findings are kept in mind. It is the purpose of these remarks to demonstrate what we consider definite diagnostic aids in the recognition of this disease.

CLINICAL FEATURES

Incidence

Hepatoma most often occurs between forty and sixty years of age, although it is rarely seen in early childhood and occasionally in patients over eighty years of age. Cirrhosis, syphilis, malaria, alcoholism and parasitic infections in the liver are said to be causative factors. The majority of cases are found in males possibly because of the higher incidence of cirrhosis in this sex. It would appear that primary carcinoma of the liver is a disease controlled by racial and not environ-

* From the Department of Medicine, Section of Gastro-enterology, New York Medical College, Flower-Fifth Avenue and Metropolitan Hospitals' Service.

† Associate Professor of Medicine and Head of Section of Gastro-enterology, New York Medical College, Flower and Fifth Avenue Hospitals.

‡ Fellow in Internal Medicine, New York Medical College, Flower and Fifth Avenue Hospitals; Resident in Medicine, Metropolitan Hospital.

of the liver capsule. Pain is slight if the growth is deep-seated and most severe if the growth has spread to the diaphragm or to Glisson's capsule.

An otherwise unexplainable mild *fever* is rather characteristic. The temperature rarely rises higher than 103° F. It is irregular in nature. Chills are never present. Sweating is scant or absent.

Ascites is a very constant feature and is often hemorrhagic in nature. The jaundice is usually mild. *Hepatomegaly* is found in 50 per cent of the cases. After paracentesis, the nodularity of the tender liver can frequently be palpated. There is a moderate *loss of weight*, which may be unsuspected by the patient because of retention of fluid. Dilated vessels on the abdomen are above the umbilicus and caput medusae is absent. Portal vein thrombosis and hematemesis secondary to ruptured esophageal varices are terminal features.

Other symptoms occasionally seen are vague gastro-intestinal complaints, thin drawn facies, edema of lower extremities and some change in bowel habits. The duration of the illness is always characteristically short. Most cases are fatal after several months.

LABORATORY DATA

An analysis of the laboratory data is very interesting and in our opinion quite valuable in making the diagnosis.

Leukocytosis is variable, the white blood count ranging from 3000 per cm. to 44,000 per cm.

There is always some manifestation of impairment or abolition of one or many of the metabolic functions of the liver.

The *bromsulfalein test* constantly shows retention of more than 20 per cent of dye. *Total proteins* may be normal, though the albumin-globulin ratio is frequently less than 1. This is important in evaluating the pathogenesis of the ascites.

Total cholesterol may be lowered, normal and sometimes slightly elevated, depending on whether the obstructive features predominate over the parenchymal impairment.

The *cephalin flocculation test* has been reported to be par-

mental factors. It occurs very frequently in both dark-skinned (Negro and yellow [Mongolian]) branches of the human stock. Moreover, among some pigmented races (Bantu and Javanese) it is undoubtedly the most common neoplasm encountered. Though the incidence of cirrhosis in the latter races is high, the figures do not seem to be large enough to form in themselves a sufficient explanation for the frequency of primary liver carcinoma, which in Europe and United States develops in a small percentage of patients with cirrhosis of the liver.[1, 2]

Classification

C. Berman,[1] who has probably seen the largest group of cases in the Bantu races of South Africa, classifies his cases on a symptomatologic basis into the following categories: (1) "frank" carcinoma (64 per cent) where the signs and symptoms are referred to the liver from the onset in a patient in previously good health; (2) acute abdominal carcinoma (9 per cent) in patients with latent primary carcinoma of liver who suddenly develop an acute surgical abdomen following rupture of carcinomatous nodules or erosions of blood vessels on the free margin of the liver; (3) febrile group (3.6 per cent) in patients with rapidly growing tumor of liver and clinical manifestations resembling hepatic abscess; (4) metastatic carcinoma (4.6 per cent) in which symptoms of metastasis completely overshadow the primary lesion.

Symptoms

Among the symptoms, *asthenia* is rather predominant and is somewhat characteristic. The weakness is only experienced shortly before admission to the hospital and is the symptom which usually forces the patient to seek treatment. Once present, it becomes alarmingly progressive, so that the patient is forced to bed and remains there.

The *pain* is dull, aching and localized to the right hypochondrium. Though constant in character, it is more marked on exertion and without relationship to food. The pain increases in severity due to perihepatitis or to rapid stretching

itoneum can be determined. It is frequently possible to distinguish between a normal and cirrhotic liver or one studded with metastatic nodules. Under the direct field of vision of the peritoneoscope, biopsy specimens of the liver can be obtained for histologic examination. Although we have not employed peritoneoscopy in any of our cases of primary liver carcinoma, it would seem that in those cases where it can be done without too much difficulty, it may be of considerable aid in diagnosis.

Aspiration liver biopsy over a palpable nodule has been employed in most of our cases and the pathologist has always been able to diagnose the presence of carcinomatous cells.

DIFFERENTIAL DIAGNOSIS

Malignant Disease of Other Organs with Secondary Liver Involvement.—Secondary malignant disease of the liver, particularly from lesions of the stomach, right and transverse colon, right kidney and adrenal gland, pancreas and gallbladder, must be considered. *Gastric carcinoma* usually gives a more typical history related to this organ, and is characterized by the presence of a "doughy" abdomen, marked tenderness in the epigastrium, palpable gastric tumor, pyloric obstruction and characteristic gastric contents. *Right kidney* and *adrenal tumors* are usually palpated in the flank and costovertebral region; the tumors are more ballotable, and can be demarcated from the liver itself. Adrenal tumors sometimes have associated endocrinopathic features. Carcinomas of the right and transverse *colon* are usually characterized by marked secondary anemia, with a milder and more prolonged course; the tumor is connected to the large intestine, is only slightly movable with respiration and may be separated from the liver edge. Pancreatic tumors may be associated with signs of pancreatic deficiency, the patient is less toxic and the course is longer. Islet tumors of the *pancreas* can be differentiated from the hypoglycemic syndrome of primary hepatic carcinoma by the absence of severe liver damage that is seen late in the latter disease.[10] Carcinoma of the fundus of the *gallbladder* affects women in the ratio of 5 to 1 in the man. Although symptoms of gallstones are absent in the

ticularly valuable in determining active parenchymatous damage to the liver.[3, 4] It has been found to be positive in the serum of all patients with acute hepatitis, in cirrhosis and chronic passive congestion, and that clinical improvement accompanies the decrease in the flocculation reaction. In the serum of patients with carcinomatous involvement of the liver, the reaction seems to be related to the extent of malignant involvement. In primary liver carcinoma, it may or may not be positive.

Alkaline phosphatase seems to be very significant in primary liver carcinoma. If one excludes pathologic bone conditions such as Paget's disease and metastatic bone disease, elevation of alkaline phosphatase is usually associated with obstructive disease of the liver. Gutman and associates[5] in their cases of primary carcinoma of the liver have noted an alkaline phosphatase above 10 Bodansky units regularly. It has been shown that increased serum phosphatase activity without hyperbilirubinemia can occur in incomplete obstruction. One theory offered is a decreased permeability to serum phosphatase in the kidney as compared with the excretion of bile pigments.[6] However, Kabat and Furth,[7] utilizing a histochemical method for identification of phosphatase in the tissues have studied sections of primary carcinoma of the liver in rats and have found that the cancer cells, especially the endothelial cells between the newly formed, ductlike structures contained large amounts of phosphatase, while those of the sinuses of relatively normal liver tissue contained none or only traces. Thus, there is experimental evidence that carcinoma cells in the rat are rich in phosphatase. Regardless of the mechanism, it is our belief that an elevated alkaline serum phosphatase without other chemical evidence of obstruction in the liver is diagnostic for malignancy in the liver.

SPECIAL DIAGNOSTIC MEASURES

Peritoneoscopy,[8, 9] a procedure whereby the examiner can obtain an endoscopic view of the abdominal cavity has been employed with increasing frequency in our clinic during the last two years. In properly selected cases, the presence or absence of metastasis to the liver, spleen, omentum and per-

chromatosis is suggested whenever any or all of the following occurs: a symptom complex of short duration and rapid progression; abdominal pain; jaundice; a markedly enlarged liver which extends upward and is extremely hard and grossly nodular; rapidly recurring sanguineous ascites; sudden amelioration of the diabetes and/or liability to hypoglycemic intervals; fever; anemia; leukocytosis; weight loss; evidence of metastatic involvement, especially in the lung.

Acute Surgical Abdomen.—The ease with which highly vascular and friable metastatic growths in the liver rupture and produce hemoperitoneum frequently suggests the picture of an acute surgical abdomen. Many such cases have been diagnosed as intra-abdominal vascular apoplexies and thromboses, acute obstructions, and so on, but on operation, bleeding tumors of the liver have been found. The importance of an adequate history, palpable nodular liver and laboratory data can aid in the differentiation, but if the patient is first seen in the acute phase, laparotomy is perhaps indicated.

Tertiary Syphilis of the Liver.—Tertiary syphilis of the liver can be distinguished by the luetic history, positive Wassermann test, and evidence of gumma elsewhere; the predominant involvement is in the left lobe of the liver which becomes multilobular in character (so-called "hepar labatum"). The gumma is on the liver surface and may be felt as irregular rounded masses which are not umbilicated. The clinical course is milder and more protracted. The response to potassium iodide therapy is almost specific.

PROGNOSIS

Patients with untreated primary carcinoma of the liver never survive more than four months. This may be due perhaps to interference with hepatic detoxification and other metabolic functions of the liver. Berman has found twenty-eight cases reported in the literature in which attempts have been made at radical cure. In these, eight deaths occurred within sixteen days of operation, in ten instances recurrences took place within two to eight years, and in seven the patients were reported alive and well three to seven years after operation.[1]

majority of cases, when present they have preceded the tumor for three to thirty years. Gallstones are found in more than 65 per cent of the cases.[11, 12]

Roentgenologic investigations such as a gastro-intestinal series, urography, gallbladder visualization and perirenal insufflation are most helpful.

An important feature of hepatoma to be remembered is the infrequency and paucity of *distant metastasis*. The disease is characterized, rather, by extensive intrahepatic metastasis or the development of neoplasms from multicentric foci. The duration of life in hepatoma seems to be much shorter than after the appearance of secondary metastasis to this viscus.[13] Symptoms of metastasis completely overshadowing the primary lesion in the liver have been reported, but are seen in only 4.6 per cent of the total cases.[1]

In melanosarcoma of the liver, the primary site may not be determined in spite of careful examination. History of uveal tract involvement even as far as thirty years prior to the appearance of symptoms of liver involvement is reported.[14] Thormaelen's test for melanin in the urine, which turns blue black on addition of a few drops of ferric chloride solution, is frequently positive.

Cirrhosis of the Liver.—To differentiate from cirrhosis of the liver is rather difficult. Patients with cirrhosis who die are frequently found to have primary hepatoma at autopsy. A nodular liver with areas tender to palpation together with spontaneous right hypochondrial pain is ordinarily not encountered in uncomplicated hepatic cirrhosis.[10] If an atrophic cirrhotic liver starts to enlarge rapidly, a malignant condition is to be suspected. But most important, a rising serum alkaline phosphatase in the face of progressive liver damage seems to be very suggestive of a developing malignant process in a cirrhotic liver.

Berk and Lieber[15] have noted the higher incidence of primary carcinoma of the liver in *hemochromatosis* than in uncomplicated hepatic cirrhosis. It is apparently caused by the added factor of pigmentation in addition to the cirrhosis of the liver found in hemochromatosis. The authors feel that the coexistence of a primary carcinoma of the liver in hemo-

chromatosis is suggested whenever any or all of the following occurs: a symptom complex of short duration and rapid progression; abdominal pain; jaundice; a markedly enlarged liver which extends upward and is extremely hard and grossly nodular; rapidly recurring sanguineous ascites; sudden amelioration of the diabetes and/or liability to hypoglycemic intervals; fever; anemia; leukocytosis; weight loss; evidence of metastatic involvement, especially in the lung.

Acute Surgical Abdomen.—The ease with which highly vascular and friable metastatic growths in the liver rupture and produce hemoperitoneum frequently suggests the picture of an acute surgical abdomen. Many such cases have been diagnosed as intra-abdominal vascular apoplexies and thromboses, acute obstructions, and so on, but on operation, bleeding tumors of the liver have been found. The importance of an adequate history, palpable nodular liver and laboratory data can aid in the differentiation, but if the patient is first seen in the acute phase, laparotomy is perhaps indicated.

Tertiary Syphilis of the Liver.—Tertiary syphilis of the liver can be distinguished by the luetic history, positive Wassermann test, and evidence of gumma elsewhere; the predominant involvement is in the left lobe of the liver which becomes multilobular in character (so-called "hepar labatum"). The gumma is on the liver surface and may be felt as irregular rounded masses which are not umbilicated. The clinical course is milder and more protracted. The response to potassium iodide therapy is almost specific.

PROGNOSIS

Patients with untreated primary carcinoma of the liver never survive more than four months. This may be due perhaps to interference with hepatic detoxification and other metabolic functions of the liver. Berman has found twenty-eight cases reported in the literature in which attempts have been made at radical cure. In these, eight deaths occurred within sixteen days of operation, in ten instances recurrences took place within two to eight years, and in seven the patients were reported alive and well three to seven years after operation.[1]

TREATMENT

Because of the hopelessness of the disease, treatment is essentially *palliative* and directed toward the relief of pain and discomfort. Sedatives are required in large and increasingly frequent doses. X-ray and radium therapy are considered of no value in view of the rapid course of the disease.

Successful *lobectomies* are reported with survival rates as high as nine years after operation.[16] Tinker and Tinker[17] pointed out the factors favorable to safe resection of the liver:

1. The lobes and subdivisions of the liver are supplied by independent arteries; so one section can be removed without injury to the remaining sections.

2. Anastomosis between blood vessels of different lobes of the liver is free, insuring adequate circulation if a section is cut off from its normal blood supply.

3. Regeneration after removal of liver substance is rapid and quite complete.

Mann[18] emphasizes the importance of the portal circulation for restoration of the liver after partial removal.

Charache[16] feels that every case of primary tumor should be explored with the idea of possible excision of a solitary malignant tumor or even a lobectomy.

SUMMARY

1. The high incidence of primary carcinoma of the liver in the male sex between forty and sixty years of age, the usual cirrhotic background, and the predilection for the dark-skinned races are noted.

2. The clinical features of rapid onset, marked asthenia, short duration, otherwise unexplainable mild fever, ascites often sanguineous, constant dull pain in the right hypochondrium, an enlarging tender and nodular liver, leukocytosis, and the infrequent evidence of metastasis are discussed.

3. The finding of an increasing alkaline serum phosphatase without other laboratory evidence of obstructive disease in the liver is stressed and regarded as strongly suggestive for malignancy in the liver.

4. The utilization of peritoneoscopy in diagnosis is advised.

5. The differential diagnosis of primary carcinoma of the liver is discussed. That it may sometimes present the picture of an acute surgical abdomen is to be remembered.

6. Surgical excision of the tumor whenever possible is the accepted treatment at present.

BIBLIOGRAPHY

1. Berman, C.: Primary Carcinoma of Liver in the Bantu Races of South Africa. South African J. Med. Sc., 5: 54 (Oct.) 1940.
2. Bonne, C.: Cancer in Java and Sumatra. Am. J. Cancer, 25: 811, 1935.
3. Hanger, F. and Patek, A.: Cephalin Flocculation Test in Cirrhosis of the Liver. Am. J. Med. Sci., 202: 49, 1941.
4. Rosenberg, D.: The Cephalin-Cholesterol Flocculation Test in Cases of Disease of the Liver. Arch. Surg., 43: 231, 1941.
5. Gutman, A. B. et al.: Effect of Disease of the Liver and Biliary Tract upon Phosphatase Activity of Serum. J. Clin. Investigation, 19: 129–152 (Jan.) 1940.
6. Gutman, A. B. et al.: Increased Serum Phosphatase Activity without Hyperbilirubinemia after Ligation of the Hepatic Ducts in Dogs. Proc. Soc. Exper. Biol. & Med., 44: 613–617 (June) 1940.
7. Kabat and Furth: A Histo-chemical Study of Distribution of Alkaline Phosphatase in Various Normal and Neoplastic Tissues. Am. J. Path., 17: 303 (May) 1941.
8. Wershub, L. P.: Limitations of Peritoneoscopy. Bull. New York Med. College, Flower & Fifth Ave. Hosp., 4: 104, 1941.
9. Garry, W. E.: An Evaluation of Peritoneoscopy with Particular Reference to the Diagnosis of Abdominal Tumors. New England J. Med., 225: 180, 1941.
10. Boyd, L. J. and Schlachtman, M. S.: Multiple Hemorrhagic Hepatoma. Bull. New York Med. College, Flower & Fifth Ave. Hosp., 2: 110, 1939.
11. Ewing, James: Neoplastic Diseases. 4th Edition. W. B. Saunders Co., Philadelphia, 1940. p. 757.
12. Liebowitz, H. R.: Primary Carcinoma of Gallbladder. Am. J. Digest. Dis., 6: 381, 1937.
13. Greene, J. M.: Primary Carcinoma of the Liver. Internat. Abstr. Surg., 69: 231, 1939.
14. Reinstein, H.: Melanotic Sarcoma of Liver. Bull. New York Med. College, Flower & Fifth Ave. Hosp., 3: 136 (Oct.) 1940.
15. Berk, J. E. and Lieber, M. M.: Primary Carcinoma of the Liver in Hemochromatosis. Am. J. Med. Sci., 202: 708, 1941.
16. Charache, H.: Primary Carcinoma of the Liver. Am. J. Surg., 43: 96, 1939.
17. Tinker, M. B. and Tinker, M. B., Jr.: Resection of the Liver. J.A.M.A., 112: 2006, 1939.
18. Mann, F. C.: The Portal Circulation and Restoration of the Liver after Partial Removal. Surgery, 8: 225, 1940.

DYSFUNCTION OF THE GALLBLADDER AND BILE DUCTS*

MICHAEL LAKE, M.D., F.A.C.P.†

CHOLECYSTITIS with or without stones is extremely common, especially in women after the third decade, when it is said to occur in over 24 per cent of those who complain of "chronic dyspepsia." It is present in over 9 per cent of men over forty with similar complaints.[1] Autopsy records show that gallstones are found in more than 20 per cent of women and about 10 per cent of men after the age of thirty-nine. Some studies[2,3] even claim that from 50 to 60 per cent of all adults show evidence of cholecystitis, but—as Graham[4] has pointed out—since pathologists disagree as to what constitutes cholecystitis, especially after middle age, these figures may be open to question.

ORIGIN OF BILIARY COLIC

Since gallstones occur, according to these figures, almost as frequently in the general population of the same age as in this "dyspeptic" group, it seems reasonable to doubt that the symptoms of these patients are always due to their gallbladders. This skepticism is given support by the not infrequent lack of symptomatic relief from operation on patients in whom no history of colic has been obtained.

It is also true that biliary colic occurs in only a small fraction of people with gallstones—perhaps not more than 5 per cent[5]—and that symptoms not distinguishable from biliary colic may occur without evidence at operation or autopsy of any pathologic changes in the gallbladder. The pain may

* From the Department of Medicine, Cornell University, and the New York Hospital.

† Instructor in Medicine, Cornell University Medical College; Associate Physician, Midtown Hospital; Physician to Outpatients (Gastro-enterology), New York Hospital.

persist after cholecystectomy. Although the obvious explanation for some of these failures would be that the pain did not originate in the biliary tract, many excellent observers have thought otherwise.

Evidence that pain may originate in a *normal* biliary tract has been obtained chiefly from three sources:

1. Studies on the filling and emptying of the gallbladder and of the pressure relations of bile secretion, gallbladder contraction and resistance at the lower end of the common duct.

2. Pressure studies and x-ray visualization of the common duct after cholecystectomy. (It has been demonstrated that in the absence of the gallbladder, pain may occur when the sphincter of Oddi is in spasm, and can be relieved by causing it to relax.)

3. One observation by Ivy,[6] made on himself during an attack simulating biliary colic which was caused in a normal gallbladder when a secretin-cholecystokinin mixture was injected intravenously. Under the conditions of Ivy's experiment, the flow of bile into the duodenum ceased, while a copious flow of pancreatic juice was obtained. When the duodenum was flushed with magnesium sulfate the pain was relieved and dark bile appeared in the duodenum. Ivy thought this pain was due to a spastic obstruction in the common duct, with simultaneous contraction of the gallbladder. His observation suggested that in man, as in the guinea pig, there may be a separate sphincter at the junction of the common duct with the ampulla which is able to shut off the flow of bile while pancreatic secretion continues to be discharged into the duodenum.

There are no published observations of the human gallbladder during an attack of biliary colic. Recently, I have had the opportunity of visualizing the organ by x-ray during several such attacks.[7] and am able to state that it was greatly distended and continued to increase in size as long as the pain persisted.

BILIARY DYSKINESIA

It seems to be fairly well established, then, that functional disturbances of the biliary tract can cause an attack of biliary colic in the absence of stone or inflammation, and that the great majority of people with gallstones and some degree of cholecystitis do not have such attacks. Although these disturbances may be of secretion or absorption, or may depend

on changes in the character of the liver bile, good evidence exists today chiefly for the motor type of dysfunction. the so-called "biliary dyskinesia."

These facts have led to speculation along several lines. We might ask whether these functional disorders eventually result in organic changes in the biliary tract, or cause stones to form. Do they accompany and cause the symptoms in patients with gallstones or cholecystitis? Or is dysfunction a purely nervous disorder which has no relation to the frankly diseased gallbladder, just as the irritable colon has no certain relation to ulcerative colitis? These questions cannot at present be definitely answered, because our knowledge of the physiology and pathology of this region is inadequate.

Physiologic Considerations

What is actually known about the physiology of the gallbladder and bile ducts, and about the conditions under which gallstones and biliary colic occur? Although our knowledge of the physiology of the extrahepatic biliary tract has greatly increased during the past decade, it is still very incomplete, and much of it is speculative. There are several excellent recent reviews[5, 9, 10] which I shall not attempt to duplicate. Perhaps, however, an attempt to correlate some of our present information may be useful in advising our patients how to avoid gallstones, or, if they exist, how to avoid attacks of biliary colic.

1. The liver probably secretes bile continuously, although the rate of secretion varies with the kind of food eaten. This bile is alkaline. The secretory pressure of the liver does not exceed 300 mm. of water. When pressure within the ducts exceeds this, the secretion of bile ceases.

2. The sphincter of Oddi is normally closed in the fasting state, blocking the entrance of bile into the duodenum. It can normally withstand a pressure of about 120 mm. of water, but in abnormal states may withstand a pressure of as much as 750 mm.—in part due to the contraction of the duodenal muscle which surrounds it.

3. As the liver bile reaches a closed sphincter of Oddi, pressure within the common and hepatic ducts rises, and bile enters

the gallbladder through the cystic duct. During fasting, therefore, the gallbladder becomes gradually distended. A competent sphincter of Oddi is necessary for gallbladder filling.

4. The gallbladder mucosa rapidly concentrates bile six to ten times, by absorbing chiefly water and inorganic salts. When the maximum concentration of total solids in the bile constitutes about 25 per cent of the contents, the gallbladder cannot concentrate the bile further. This process is so rapid that the mere passage of bile through the gallbladder increases its concentration about five times. The alkalinity of bile is reduced in this process. The organ also secretes a thick mucinous material which makes the bile more viscid. The bile ducts do not normally concentrate, but dilute bile with a thin watery fluid.

5. When a meal containing fat or protein reaches the upper intestine, a hormone—cholecystokinin—enters the blood stream and causes the gallbladder to contract and the sphincter of Oddi to relax, so that concentrated gallbladder bile enters the duodenum. A nervous mechanism also exists for this purpose, but is not essential, as the emptying takes place readily in response to fats even after all nervous connections have been severed.

The gallbladder empties by a contraction of its wall, and not simply by a release of pressure in the common duct. It is able to retain its contents, even if the sphincter of Oddi is relaxed, or its influence removed by suturing a catheter into the common duct. There is some evidence that a sphincter also exists in the cystic duct, but this has not been established.

A gallbladder contraction exerts a maximal pressure of about 250 to 300 mm. of water, enough to open a normal common duct sphincter, but less than is needed if the sphincter is abnormally spastic. This pressure is also slightly less than the secretory pressure of the liver.

There is cholecystographic evidence that occasionally these conditions are reversed so that gallbladder contents may enter the hepatic duct. Thus, Copleman and Sussman[11] have recently reported four cases in which the hepatic duct was visualized following cholecystography, after the high-fat meal. They suggest that these findings may be confirmatory evidence of biliary dyskinesia. I also have seen one such case (Fig. 146). The patient was having no pain when these pictures were taken.

Case I.—A forty-three-year-old truck driver complained of a sticking pain to the right of the umbilicus at intervals for twelve years. More recently he also had a cramplike pain along the right costal margin, and belching. He was worse after fried foods, and better if he lay on his abdomen. The pain was never very severe. He has had no fever or jaundice. Gastric analysis (fasting): free hydrochloric acid, 50; total, 36.

Biliary drainage: A good B fraction was obtained on the second attempt, only yellow bile on the first. No crystals were present.
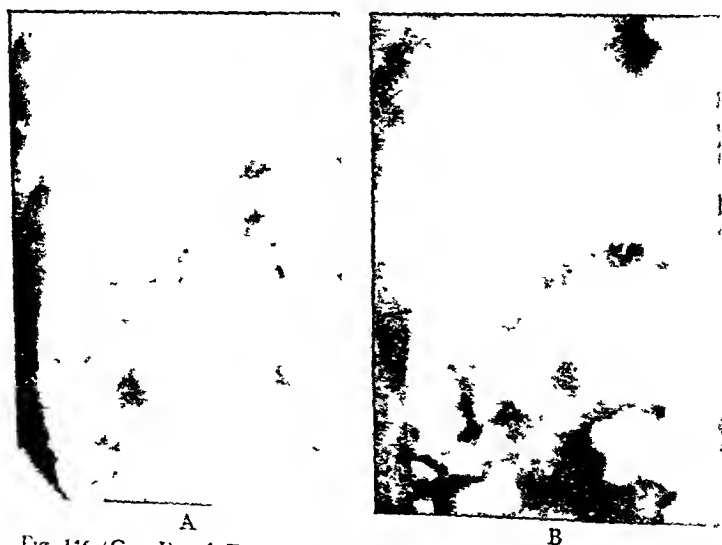
Fig 146 (Case I) —*A*, Fourteen hours after Graham dye, *B*, one hour after a high-fat meal.

A gastro-intestinal x-ray series was essentially negative except for slight tenderness over the cecum and a spastic descending colon. There was a smooth irregularity on the greater curvature of the duodenal cap which resembled a fold or band, rather than an ulcer.

One must question whether this is good evidence of dyskinesia—that is, failure of the common duct to open when the gallbladder is contracting. Since the maximal pressure exerted by a gallbladder contraction is so nearly the same as the secre-

tory pressure of the liver, we would expect that occasionally such a reversal could normally occur if the passage to the duodenum is closed. Since the normal flow of bile is momentarily shut off[12] when there is a peristaltic contraction of the duodenum in the region of the ampulla, it is possible to assume that the photograph was taken at the moment when this normally occurred and that it recorded an unusual, but not abnormal, finding. However, in our case two pictures were taken in the course of ten minutes and the examination was repeated two days later. All films taken after the meal showed this appearance. The common duct was not seen. This would indicate more than a momentary occlusion of the duct, whether by sphincteric or duodenal spasm, and by definition would have to be considered a motor dysfunction of the hypertonic variety. However, the films taken before the meal showed an L-shaped gallbladder shadow with a sharp indentation on its medial surface, suggesting that a band may be present in this region. The appearance of the duodenal cap also suggested the possibility of a band.

It is probable, therefore, that a band extended from the gallbladder across the common duct and occluded the duct when the gallbladder was contracting. Whether or not this was true, the hepatic duct must have been distended by a pressure which is usually sufficient, if suddenly applied, to cause pain. In the dog, pain is produced by distending the ducts with a pressure of 270 mm. of water, just about the usual maximum pressure of a gallbladder contraction. I suspect that many cases of "dyskinesia" have some such anatomical explanation.

FACTORS RESPONSIBLE FOR PRODUCTION OF DYSKINESIA AND FORMATION OF GALLSTONES

Factors Which Disturb Normal Function.—We see from the above summary that the *normal filling and emptying* of the gallbladder depend on:

1. A patent duct system.
2. The ability of the gallbladder to absorb water and inorganic salts rapidly so as to regulate pressure within the system, thus preventing the pressure in the ducts from increasing to a degree

which would suppress bile secretion if the sphincter of Oddi remained closed. The concentrated bile which is discharged after a meal is also useful in digestion.

3. A sphincter of Oddi which remains closed in the fasting state, which has a normal tone, and which relaxes normally when the gallbladder contracts in response to fat in the duodenum. Also a duodenum which is normally relaxed between peristaltic waves.

When the gallbladder mucosa is inflamed, it becomes unable to concentrate. The large volume of bile secreted by the liver between meals cannot be accommodated in the system, pressure in the bile ducts rises to more than the 120 mm. necessary to force the sphincter of Oddi open, and bile flow becomes continuous. This condition favors an ascending infection of the biliary tract. Or, if the sphincter does not relax at this pressure, the bile ducts dilate and stasis occurs together with back pressure on the liver, which may favor both liver damage and infection. Exactly the same thing takes place if the gallbladder is removed.

Our conception of what happens in the purely functional dyskinesias assumes that the sphincter of Oddi is in spasm, and prevents the expulsion of bile either by a normally strong gallbladder contraction or stronger than normal (hypertonic dyskinesia) or by a weak atonic contraction (atonic dyskinesia).

From a practical standpoint, therefore, we must know in order to control this condition what is apt to increase resistance at the lower end of the common duct and how to prevent this from occurring. Also, if the conception of an atonic type of dyskinesia is correct, we should know what is apt to weaken gallbladder contractions and what can be done to strengthen them.

Factors Which Increase Resistance to the Flow of Bile from the Common Duct.—It has been shown[13] that in some cases of cholecystitis and duodenal ulcer the sphincter of Oddi may be hypertrophied. In duodenitis this also probably occurs, or at least it may be rendered spastic. In *pregnancy*, gallbladder emptying is delayed, but whether this is due to increased resistance in the duct, to weakness of the gallbladder wall or to other chemical, hormonal, or reflex changes is

not known. The most common cause of gallstones would appear to be pregnancy.[14] It seems likely, also, that a functional spasm of the duct or duodenum can occur from psychic causes. I have frequently observed, in the course of biliary drainages, that the flow of bile may cease if the patient is disturbed or anxious.

Ivy and Goldman[15] demonstrated that the sphincter may be made to contract reflexly by stimulating the nerves of the colon or inferior mesenteric plexus. They also showed that distention of the colon in dogs or stimulation of the central ends of divisions of the splanchnic nerve may inhibit bile formation. This supplies a possible explanation, in the authors' opinion, as to how *constipation* may predispose to gallbladder disease. In cholangeitis,[16] the sphincter resistance may be high for some weeks after cholecystectomy; normally, sphincter resistance is decreased after cholecystectomy. Morphine and codeine are said to increase sphincter resistance,[17] perhaps by increasing duodenal tone.

Factors Which Decrease Resistance to the Flow of Bile into the Duodenum.—Fats and meats,[18] when they reach the duodenum, normally cause the sphincter of Oddi to relax and the gallbladder to contract. Fats are more effective, and also tend to decrease the tonicity of the duodenum.

Nitroglycerin, amyl nitrite, magnesium sulfate (especially if given by duodenal intubation), and theophylline are said to decrease resistance of the sphincter of Oddi.

Factors Which May Weaken the Gallbladder Wall.—Except for cholecystitis or obstruction, these factors are not known. We may assume that this may occur after a debilitating illness, in asthenic states, or perhaps when the normal stimulus for gallbladder contraction is lacking as a result of the absence of adequate amounts of fat and meat from the diet.

Other Factors Which Favor the Formation of Gallstones.—Although *stasis* may cause functional disturbances of the biliary tract, we have no certain knowledge that stasis alone can cause stones to form. In obstructive jaundice due to carcinoma of the pancreas, for example, stones are often absent. It seems likely that stasis must be accompanied by some other

changes, such as *inflammation* of the biliary tract or changes in the composition of the bile. Although there is no convincing experimental evidence that the concentration of *cholesterol* in bile changes with its concentration in the blood, clinically many of the conditions in which its blood level is high are known to predispose to gallstones. Among these may be mentioned obesity, rapid loss of weight, and pregnancy. In pregnancy the cholesterol level of the bile is also known to be high, and stasis is a factor. In typhoid fever the predominant element is *infection*, but other factors may have been formerly present, such as excessive loss of weight and possibly stasis due to debility and an inadequate diet. It would be interesting to see if more recent cases treated with a high calorie diet are as prone to this complication.

I have been impressed with the frequency with which gallbladder attacks begin after a period of *rigid dieting and marked weight loss*, usually in women who are overweight. The two cases below will serve as examples.

CASE II.—A thirty-four-year-old single woman weighing 173 pounds went on a rigid diet during which she lost 23 pounds in a few weeks. She then began to complain of regurgitation of food and abdominal discomfort. X-ray examination showed a functioning gallbladder with stones. This was confirmed by operation.

CASE III.—A thirty-three-year-old married woman who has never been pregnant, weighing 152 pounds, went on a rigid diet and for ten days ate practically nothing, excluding all fats and skipping meals. She weighed 140 pounds when seen. She then developed a "terrific, cramplike pain" about the navel, on the right side and right lumbar region which required an injection of morphine, and was accompanied by vomiting. She had been constipated for a long time. There were no urinary symptoms. All examinations were negative except for evidence of gastritis, a spastic duodenal cap, and a normally functioning gallbladder which contained stones.

Whether the stones formed in these cases during the period of dieting, or whether the first symptoms were merely initiated at that time we do not know.

In chronic hemolytic jaundice, gallstones occur in over 50 per cent of patients. Here the bile contains abnormal amounts of bilirubin, due to excessive blood destruction. I do not know of any studies which deal with the incidence of gallstones in other conditions characterized by excessive blood destruction, such as chronic malaria or pernicious anemia, but we might expect a similar tendency in these diseases.

It is well known that people with gallstones frequently have an attack of pain following an emotional upset. Here psychic inhibition of gallbladder emptying or duodenal spasm may be factors.

PRACTICAL CONSIDERATIONS IN THE HYGIENE OF THE GALLBLADDER AND BILE DUCTS

We may formulate certain preventive or therapeutic principles which in the light of our present knowledge might be logical or helpful in the management of extrahepatic biliary diseases.

1. We should correct if possible any general condition which is characterized by an abnormal concentration of cholesterol or bilirubin in the blood or bile.[19] Although laboratory data are largely lacking, we know that clinically many, but not all, of these conditions predispose to the formation of gallstones.

2. An adequate daily intake of fat or meat is necessary to prevent stasis in the biliary tract. This is particularly important during pregnancy, typhoid fever and during rapid loss of weight.

3. Any condition which results in irritation or inflammation of the duodenum should be treated.

4. Since reflex causes might interfere with the normal function of the biliary tract, irritative or inflammatory conditions of the gastro-intestinal tract should be eliminated whenever possible. Constipation should be corrected.

5. We should recognize that nervous and emotional factors may result in biliary stasis and this may precipitate attacks of biliary colic.

BIBLIOGRAPHY

1. Rivers, A. B. and Ferreira, A. E. M.: Incidence and Causes of Chronic Dyspepsia at Various Ages. J.A.M.A., *110*: 2135 (June 25) 1938.

2. Crump, Curtis: The Incidence of Gallstones and Gallbladder Disease. Surg., Gynec. & Obst., *53*: 447 (Oct.) 1931.

3. Mentzer, S. H.: A Clinical and Pathological Study of Cholecystitis and Cholelithiasis. Surg., Gynec. & Obst., *42*: 782 (June) 1926.

4. Graham, E. A.: The Clinical Application of Some Recent Knowledge of the Biliary Tract. The Harvey Lectures, 1934–35. Williams & Wilkins Co., Baltimore, p. 176.

5. Lyon, B. B. Vincent: Non-surgical Drainage of the Gall Tract. Lea & Febiger, Philadelphia, 1923, p. 432.

6. Ivy, A. C., Voegtlin, B. S. and Greengard, Harry: The Physiology of the Common Bile Duct, a Singular Observation. J.A.M.A., *100*: 1319 (April 29) 1933.

7. To be published.

8. Ivy, A. C.: Physiology of the Gall Bladder. Physiol. Rev., *14*: 1 (Jan.) 1934.

9. Mann, F. C.: Physiol. Rev., *4*: 251 (April) 1924.

10. Ivy, A. C. and Bergh, G. S.: The Applied Physiology of the Extra-hepatic Biliary Tract. *103*: 1500 (Nov. 17) 1934.

11. Copleman, B. and Sussman, M. L.: Hepatic Duct Visualization Following Oral Cholecystography. Radiology, *36*: 465 (April) 1941.

12. Lueth, H. C.: Studies on the Flow of Bile into the Duodenum and the Existence of a Sphincter of Oddi. Am. J. Physiol., *99*: 237 (Dec.) 1931.

13. Giordano, A. S. and Mann, F. C.: The Sphincter of the Choledochus. Arch. Path., *4*: 943 (Dec.) 1927.

14. Huggins, R. R., Harden, Boyd and Grier, G. W.: A Study of the Relationship of Pregnancy to Diseases of the Gallbladder. Surg., Gynec. & Obst., *61*: 471 (Oct.) 1935.

15. Ivy, A. C. and Goldman, Leon: Physiology of the Biliary Tract. J.A.M.A., *113*: 2413 (Dec. 30) 1939.

16. Doubilet, Henry and Colp, Ralph: Resistance of the Sphincter of Oddi in Human. Surg., Gynec. & Obst., *64*: 622 (March) 1937.

17. Walters, W., McGowan, J. M., Butsch, W. L. and Knepper, P. A.: The Pathological Physiology of the Common Bile Duct. J.A.M.A., *109*: 1591 (Nov. 13) 1937.

18. Best, C. H. and Taylor, N. B.: The Physiological Basis of Medical Practice. 2nd Ed. Williams & Wilkins Co., Baltimore, 1939, p. 769.

19. Twiss, J. R. and Barhard, J. H.: J.A.M.A., *111*: 990 (Sept. 10) 1938.

PSYCHOSOMATIC MANIFESTATIONS OF GASTRO-INTESTINAL DISORDERS

STEPHEN P. JEWETT, M.D.*

THE recognition of the psychobiologic unity of the human organism is one of the major contributions of psychiatry to modern medicine. A physician who attempts to interpret all the physical manifestations of disease purely in terms of organic pathology will fall far short of his diagnostic and therapeutic aims. The combined clinical, physiologic and psychoanalytic[1] approach has gradually broken down that artificial barrier which medicine so long set up between soma and psyche. In living patients we deal with psychobiologic beings in whom disturbances based exclusively upon organic pathology may manifest themselves for a time almost exclusively in psychic effects and those based upon a psychopathologic background may manifest themselves mainly in somatic form. Emotional tension, whether conditioned by stimuli from without or conflict from within, may greatly disturb physiologic functioning and eventually set up a chain of events which terminate in morphologic tissue changes. These psychologically conditioned disturbances of physiologic functioning which we term "organic neuroses" may take place in the cardiovascular system, the genito-urinary system, the respiratory system, the gastro-intestinal system, and even in the skin.

At this time we are concerned with some of those disturbances of gastro-intestinal functioning, usually referred to as *gastric* and *intestinal neuroses*, the etiologic basis of which rests upon emotional excitations of the subcortical centers

* Professor of Psychiatry and Head of Department of Psychiatry, New York Medical College and Flower and Fifth Avenue Hospitals; Visiting Neuropsychiatrist and Director of Department of Neuropsychiatry, Metropolitan Hospital.

and their conduction through sympathetic and parasympathetic pathways to the gastro-intestinal tract. A vast accumulation of clinical and experimental material irrefutably proves that personality disorders of an emotional nature frequently express themselves in such disturbances, affecting the motor, secretory or sensory functions.

Illustrative Case

In everyday clinical practice these manifestations frequently are looked upon as isolated physical phenomena and are treated as such without relating them to the underlying personality disorders and situational backgrounds of which they are but an expression. The following brief case history will illustrate this point:

A thirty-five-year-old patient was referred by a physician who had treated him for gastro-intestinal disturbances for about seven years. Any kind of food would create severe distress often accompanied by nausea, diarrhea and giddiness. Finally a state of intense apprehension was induced by any taking of food. The patient first restricted his diet, which did not help. Finally he eliminated one thing after another, thinking each in turn was the thing which disagreed, but this likewise was in vain. At the time of referral he had been reduced to such a state of weakness and malnutrition that he had to give up his work. He was quarrelsome and irritable with his wife and complained of inability to concentrate well. Attempts at movement produced feelings of giddiness and nausea. Careful questioning brought out the fact that he was irritable and worrisome for several years before the gastro-intestinal symptoms started and this was confirmed by the wife who likewise stated that for at least four years prior to the beginning of the symptoms her husband had experienced sudden attacks of acute anxiety with palpitation, giddiness, nausea and sometimes vomiting and diarrhea. Inasmuch as the gastro-intestinal symptoms were the most marked on these occasions he began to think that his stomach was the cause of all his symptoms. He had consulted various physicians, had his tonsils removed, his eyes refracted and finally, after repeated laboratory tests, a diagnosis of "spastic bowel" was made and the patient settled down to a state of accepted gastro-intestinal invalidism with drug therapy and diet as the principal measures of treatment.

Further interviews with the patient elicited the fact that shortly

after his marriage his physician had warned him that his wife's physical condition was such that pregnancy would be a very dangerous hazard, but gave him no contraceptive advice. Being the type of individual who could not discuss such matters freely, he practiced the only form of contraception which occurred to him, i.e., coitus interruptus. He had practiced this until a fairly recent date when he developed a total lack of desire chiefly because of his symptoms and finally came to consider himself impotent. Further questioning brought out the fact that prior to marriage he had experienced an attack of acute anxiety following abrupt cessation of the practice of masturbation after hearing that it was harmful to the mind.

Space does not permit further detail regarding this case other than to state that a complete disappearance of all his symptoms finally came about and he was able to return to work feeling better than he had for years. This could never have been accomplished through continued emphasis upon his gastro-intestinal symptoms instead of seeing them as only a partial expression of personality disorder of multiple causation with resultant emotional tensions and excitations of the vegetative nervous system.

Elimination of Organic Disease as Causative Factor

Certain factors in disturbed gastro-intestinal functioning should make one very reluctant about regarding them as "nervous or mental" without definite proof. Among these is the age factor. Persistent gastro-intestinal symptoms occurring for the first time in individuals past forty should make one suspect their organic nature. Definite changes in the characteristics of symptoms should make one cautious. Continued abdominal pain; persistent hyperacidity when associated with pain and heartburn; gastric pain associated with subacidity, vomiting and retention; the presence of macroscopic or microscopic blood in stool or romitus unless definitely explained by some such factor as bleeding gums, nasopharyngeal hemorrhage, or hemorrhoids; the presence of a profound anemia with or without loss of weight—all these things should make one especially careful to exclude organic disease as a causative or concomitant factor.

and their conduction through sympathetic and parasympathetic pathways to the gastro-intestinal tract. A vast accumulation of clinical and experimental material irrefutably proves that personality disorders of an emotional nature frequently express themselves in such disturbances, affecting the motor, secretory or sensory functions.

Illustrative Case

In everyday clinical practice these manifestations frequently are looked upon as isolated physical phenomena and are treated as such without relating them to the underlying personality disorders and situational backgrounds of which they are but an expression. The following brief case history will illustrate this point:

A thirty-five-year-old patient was referred by a physician who had treated him for gastro-intestinal disturbances for about seven years. Any kind of food would create severe distress often accompanied by nausea, diarrhea and giddiness. Finally a state of intense apprehension was induced by any taking of food. The patient first restricted his diet, which did not help. Finally he eliminated one thing after another, thinking each in turn was the thing which disagreed, but this likewise was in vain. At the time of referral he had been reduced to such a state of weakness and malnutrition that he had to give up his work. He was quarrelsome and irritable with his wife and complained of inability to concentrate well. Attempts at movement produced feelings of giddiness and nausea. Careful questioning brought out the fact that he was irritable and worrisome for several years before the gastro-intestinal symptoms started and this was confirmed by the wife who likewise stated that for at least four years prior to the beginning of the symptoms her husband had experienced sudden attacks of acute anxiety with palpitation, giddiness, nausea and sometimes vomiting and diarrhea. Inasmuch as the gastro-intestinal symptoms were the most marked on these occasions he began to think that his stomach was the cause of all his symptoms. He had consulted various physicians, had his tonsils removed, his eyes refracted and finally, after repeated laboratory tests, a diagnosis of "spastic bowel" was made and the patient settled down to a state of accepted gastro-intestinal invalidism with drug therapy and diet as the principal measures of treatment. Further interviews with the patient elicited the fact that shortly

temporary relief is obtained they unwittingly add to their discomfort by the introduction of more air into their stomachs than they expel and repeat the procedure over and over until a habit is formed.

Such a simple explanation hardly fits all cases. In many instances of aerophagia which the author has observed the phenomenon had all the characteristics of a tic accompanied by all the evidence of narcissism displayed in such cases. It is exceptionally rare for an individual to seek treatment for this condition as such, partly because he does not know he is an air swallower and hence does not regard the condition as significant.

Rumination or Merycism

This condition, like air swallowing, is, on the surface at least, usually acquired quite incidentally. Deeper investigation frequently reveals the oral gratification bound up in the performance. In any event, it gradually assumes the characteristics of a habit. While it is chiefly encountered in children, it occasionally occurs among adults.

During the act, food is brought up from the stomach without any feeling of disgust, nausea or retching. The food is sometimes rejected, but is more often rechewed and swallowed. It is probably significant that the habit is found more frequently among emotionally deprived children.

Regurgitation

This differs from rumination in that the food which is regurgitated involuntarily without nausea is always rejected. While as a symptomatic expression of a neurosis it is rather rare, when it does occur as such it usually persists throughout the entire period of digestion.

Hypermotility

While this may occur as a purely "nervous" manifestation, the frequency with which it is associated with organic disease of the gastro-intestinal tract should cause one to exercise great caution before considering it as such.

Evaluation of the Patient's Complaints

After organic disease of the gastro-intestinal tract, as well as disease of any of the accessory organs of digestion and of other systems which might reflexly cause the symptoms, have been excluded, one should not lightly dismiss the complaints as "just due to nervousness." It is necessary to analyze carefully the nature of the nervousness and to investigate the cause of the same. "Nervousness" signifies many things to many persons and is a term too loosely used by many of the medical profession. It may mean anything from the habitual tenseness of a high-strung individual, to the more serious manifestations of one of the minor or major psychoses. A careful study of the personality of the patient becomes far more important in many gastro-intestinal cases than a constant repetition of laboratory tests, as valuable as the latter are when used with good judgment and discretion.

GASTRO-INTESTINAL SYMPTOMS OF NERVOUS ORIGIN

It is again emphasized that it is only for convenience that gastro-intestinal symptoms of "nervous origin" are referred to as though they occurred in practice purely as isolated phenomena. Treated in this way they may be divided into disturbances of (1) motor functioning, (2) secretory functioning, and (3) sensory functioning. Actually they usually occur as mixed forms and no further attention will be paid to this classification. There follows a discussion of the various manifestations in which these gastro-intestinal symptoms may appear.

Air-Swallowing, Eructatio Nervosa or Aerophagia

Air swallowing as a "nervous" reaction or "habit" is occasionally met with in both adults and children. Certain nervous individuals, following eating which may have been performed too rapidly or with insufficient chewing, experience a feeling of tension in the stomach. In order to "bring up the gas" they go through certain movements in which the abdominal walls and diaphragm are put on tension and the whole performance is ended with a peculiar sound. While

tain substances from a mixed meal, the indifference with which the individual tolerates the vomiting, and finally, the frequent association of the vomiting with both internal and external situations which affect the mood.

Cardiospasm

By this is meant a spasmodic contraction of the cardia. We are not concerned here with those cases in which definite anatomic lesions can be demonstrated in the lower end of the esophagus or the cardiac end of the stomach. These lesions naturally should be excluded before designating the symptoms as part of a neurosis. It must always be held in mind, however, that an individual suffering with organic disease of the gastro-intestinal tract may have symptoms not directly correlated with the same which may be of nervous origin.

Bad eating habits, particularly the swallowing of food that is too hot or too cold or some emotional state of great intensity may precipitate an attack of cardiospasm in a neurotically disposed individual. It may occur in an acute form lasting from a few hours to a few days or as a chronic condition. Preceding an acute attack swallowing is painful and difficult, and a burning sensation is usually found behind the sternum often attended by a feeling of fullness. Shortly the regurgitation of undigested alkaline food appears and the symptom disappears. In the chronic form there is a more or less constant condition of dysphagia attended by great difficulty in swallowing anything excepting small quantities of soft foods or liquids. Intermittent regurgitation may take place and there is a more or less continuous feeling of substernal discomfort.

Pylorospasm

This term is applied to spasmodic contractions of the pyloric sphincter of nervous origin. It occurs in certain vagotonic types of individuals under conditions of nervous tension. As a rule it takes place only at irregular intervals and persists but a short time in the beginning, and usually two or three hours after a meal. There are associated cramplike pains in the vicinity of the pylorus. Finally in persistent cases periodic attacks of vomiting occur.

Nervous Vomiting

We are not concerned here with cerebrospinal vomiting which is due to central stimulation of the vomiting center in the medulla caused either by injury or disease of the central nervous system, nor with reflex vomiting which is caused by impulses carried to the vomiting center by disease of organs even remote from the stomach, although both of these forms are sometimes referred to as "nervous vomiting."

True nervous vomiting may occur as a more or less isolated phenomenon in reaction to certain specific situations in some emotionally unstable persons or more frequently as one of many other expressions of a neurotic illness. It presents its greatest problem in children.

The diagnosis of this condition is not always easy. Special caution should be exercised in not confounding it with cyclic vomiting in children which has a definite physiogenic origin. Perhaps the most important single clue is the occurrence of other "nervous" symptoms either simultaneously or between attacks. Other clues are certain facts found in the history, such as (1) faulty feeding habits in which there was much gagging, retching, and vomiting usually accompanying the forcing of food in an atmosphere charged with tension and anxiety during which the vomiting mechanism was so frequently touched off that it became an established pattern during latter times of tension and excitement; (2) the presence during a considerable portion of the early life of a child of an adult who vomited frequently, which furnished a pattern for imitation; (3) frequent occurrence of gastro-intestinal upsets associated with vomiting during which the child was the object of a great deal of anxiety and concern and which he automatically learned to utilize as an outlet for later personality disturbances; (4) vomiting closely associated with school and which ceases week-ends and vacations; (5) where some unusually intense situation such as witnessing a person being killed once provoked vomiting and some similar situation witnessed brings up a strong association of ideas; (6) certain characteristics surrounding the act of vomiting or in connection with it, such as the fact that sometimes indigestible substances are retained, the selective ejection of cer-

and by the presence of known nervous instability in the patient.

Hyperchlorhydria

In spite of the fact that hyperchlorhydria is so frequently associated with organic disease and particularly as a reflex phenomenon from diseased conditions of the abdomen outside the stomach, in a large number of cases it occurs as one of the manifestations of a neurosis or psychosis.

Hyperesthesia and Paresthesia of Stomach and Bowels

Sensations of "all-gone feeling," churning, crawling, fullness, burning, soreness, as well as other disagreeable feelings, often accompanied by actual generalized or localized tenderness but without rigidity frequently are the subjects of complaint by psychoneurotic patients, particularly those suffering from anxiety states. Likewise, patients suffering from any of the serious types of depressions, especially the reactive or involutional-hypochondriacal types, are prone to display marked preoccupation with their bodily organs and not infrequently complain of localized and generalized abdominal discomforts of the kind described above. Such cases have frequently become the victims of much needless surgery and finally come to the psychiatrist's attention with their original complaints only after repeated operations over periods of years. In the absence of clear-cut evidence of organic disease of the gastro-intestinal tract or the accessory organs of digestion, a patient complaining of such hyperesthesias and paresthesias should have careful consideration of his emotional and mental condition.

Miscellaneous Gastro-intestinal Symptoms of Nervous Origin

It is quite impossible to cover the entire range of gastro-intestinal symptoms of "nervous" origin in this short article. Among a few which have not been mentioned are certain instances of *chronic constipation* which originate on the basis of personality disorder. It is only necessary to mention the "closer pedant" who lessens the sensitivity of the rectal nerves with his "habits" or the individual who is so "bowel"

The diagnosis of pylorospasm of nervous origin never should be made except when proper roentgenologic and other tests definitely have excluded disease within the gastrointestinal tract. Even then one should be cautious about making it unless evidence of neurotic illness is also present.

Gastric Atony

Occasionally the normal tone of the musculature of the stomach becomes lost through vagal inhibition or sympathetic stimulation to the point that atony takes place. Prolonged anxiety and other psychic disturbances in sympathotonic individuals may produce the condition.

Symptomatically it is expressed by diminished appetite and feeling of marked distention. Ingestion of only small quantities of food is often accompanied by belching and sour eructation. Finally dilatation takes place. The patient usually is constipated.

Intestinal Spasm

Increased peristalsis or irregular contractions of the bowels or parts of it, resulting in distress, gurgling of gas and sometimes passage of feces occurs without organic disease and as a nervous manifestation. In chronic cases spastic constipation takes place.

The diagnosis rests on the above symptoms, the unquestioned establishment of other signs of neurotic illness and the exclusion of correlated organic findings.

Peristaltic Unrest (Tormina Intestinorum Nervosa)

Excessive peristalsis of the small intestine which is visible, palpable and accompanied by loud rumbling sounds is occasionally seen in certain nervous subjects. Such attacks may last from a few minutes to a few hours and usually are initiated by some emotional disturbance.

This condition is not dangerous, though very disagreeable and often alarming to the patient as well as to the physician when observed for the first time. It is to be distinguished from the early stages of intestinal obstruction by absence of pain, vomiting, constipation, tympanites and changes in pulse

leave the basic etiology untouched and the patient more firmly fixed in his neurosis than when the treatment began.

It is to be remembered that a majority of the patients who suffer from these organic neuroses are entirely unaware of their psychic origin. Therefore, one important function of the treatment procedure is *to help bring about such an awareness* so that fundamental therapy can be carried out. This is often an extremely difficult thing to do and the matter has to be handled with much wisdom and good judgment. Certainly some of the more common practices should be avoided, such as bluntly informing the patient that his symptoms are "just mental." Such explanations may be taken by the patient to mean that he is only imagining that he is suffering, or even something worse. It will result in lessened confidence in the physician and help to create deeper resistance than he already has concerning the real origin of his distress. The physician must always acknowledge the reality of the symptoms as well as the reality of the suffering but should explain that they have no organic cause. He then may carefully show by simple illustrations how disturbed emotions can create physical symptoms. This he usually can accomplish by giving one or two common examples of how fear, anger and other emotions can bring about physiologic changes, and gradually lead to a better understanding of how deeper psychic disturbances can operate in creating profound visceral symptoms.

If the physician will keep in mind one of the cardinal principles of psychiatric technic, namely, that the taking of the "complaint" and the history is not only a part of the examination but *a highly important part of the treatment procedure*, he will not play the role of an inquisitor only, but will go a long way in letting the patient himself spontaneously and quite unwittingly in many instances set the proper stage for an explanation of the true nature of his disorder.

Medication

While the more superficial palliative and supportive measures in the form of drugs and other physical measures are quite indispensable in many cases of these organ neuroses, a word of caution should be uttered concerning the very in-

conscious and so preoccupied with the idea of the dire consequences to his health which will ensue upon his failure to have a daily movement of his bowels that he develops the cathartic habit. In both these instances as well as in many similar ones a psychiatric study will frequently reveal an individual with definite signs of an obsessional character or of an actual obsessional neurosis which furnishes the fundamental basis for the symptoms.

Nor should we forget to consider certain special types of *mucous colitis,* in which, though the patient is constipated. there is a more or less profuse discharge of mucus attended with colicky pains which almost always occur on the basis of a prolonged anxiety tension state.

Anorexia nervosa should always be considered as a manifestation of an underlying personality disorder and treated on this basis.

TREATMENT

Space permits no detailed discussion of the basic therapeutic procedures necessary in these organic neuroses, nor of the more superficial symptomatic and palliative measures in the form of drugs, physical therapy and the like. We can only point out certain general principles which should guide one in their intelligent management.

Psychiatric Approach

Inasmuch as the disturbances of gastro-intestinal functioning which have been outlined are actually but manifestations of some underlying personality disorder, expressed though they be in somatic form, the basic therapy should follow psychiatric lines. This does not mean that all such cases of organic neuroses should be turned over by the internist to one more experienced in psychiatry, but it does mean that the physician who does handle them should be so familiar with the psychogenesis of such organ disturbances that he does not fall into the trap which the patient himself usually does and set up hypothetical physical bases for their causation when none in fact can be found. If he does make this mistake, he will fall into another error in the form of beginning and ending his treatment with symptomatic therapy and

TRACTION DIVERTICULUM OF THE ESOPHAGUS

ROBERT P. WALLACE, M.D.*

TRACTION diverticulum of the esophagus in association with severe complications such as mediastinal abscess and bronchial fistula with pneumonia or gangrene has been noted by pathologists as a cause of death. Uncomplicated, the diverticulum exists as an autopsy curiosity, and it is not often realized that the diverticulum may cause symptoms during life prior to the onset of a complication. This fact was emphasized in the report of ten cases discovered during life by Sturtevant, Shapiro and Wallace, and stress was given to the point that when a proper contrast medium was used visualization of the diverticulum by means of the fluoroscope was not difficult or unsuccessful.

Twenty-six cases, discovered and analyzed, were reported by the writer. This series has now increased to forty. *Symptoms* were directly due to the diverticulum in 38.5 per cent, and in most instances constituted the chief complaint. For the most part the symptoms were mild and consisted of pain behind the sternum, burning or a sensation of heaviness. Usually the pain was referred to the midsternal region, but when severe was not localized. There was no constant radiation of the pain. Dysphagia was a common symptom, and swallowing was not only painful but difficult. Gross hemorrhage from the diverticulum, with or without melena, occurred in three cases, the remainder of the upper gastro-intestinal tract being free from disease.

The average age of the twenty-six patients was fifty-five years, and the frequency of incidence was equal in the two sexes. In approximately two thirds the long axis of the sac

* Assistant Clinical Professor of Medicine and Physician-in-Charge of Gastro-intestinal Clinic, New York University College of Medicine; Assistant Visiting Physician, Third Division, Bellevue Hospital.

discriminate use of sedatives, antispasmodics, analgesics and other drugs which is so often made. They should never be given at all if they can be dispensed with nor used longer than the exigencies of the situation require. Before prescribing them, the patient should always be informed that they are not given as a cure but merely for the relief of the most distressing symptoms while the more basic treatment can be carried out.

before esophageal tonus is sufficiently relaxed for the barium to enter the sac, and filling seems to occur by back pressure.

The importance of employing a *proper contrast medium* cannot be overemphasized. A proprietary opaque medium, Rugar, after conscientious trial, has not given such consistently satisfactory results as a freshly prepared barium-mucilage of acacia mixture. By means of a metal spoon and a stout cup the mucilage is vigorously mixed with powdered barium until a homogeneous semiliquid is obtained. The desired consistency may show considerable variation with the preference of the examiner. A mixture thin enough to flow in a slow, continuous, sticky stream results in better visualization than one which drops from the spoon in chunks. The correct medium produces a dense shadow, necessitates 1 teaspoonful for examination of the entire esophagus in each plane and is swallowed piecemeal.

In order to demonstrate the type and severity of the symptoms customarily encountered, four of the forty cases are presented:

ILLUSTRATIVE CASES

CASE I. MILD SYMPTOMS.—The patient is a forty-five-year-old man, who was formerly an habitual and excessive drinker of whiskey. Suspecting this to be the cause of his illness he abstained from drinking but without relief. There had been eight or more admissions to other hospitals for attacks of a burning sensation in the upper abdomen, hiccough, and a heaviness in the left chest. The chest pain was vague, occasionally substernal, and at rare times was aggravated by eating. The only clinical findings were three small diverticula, one above the other, located in the mid-third of the esophagus with the long axes directed to the left anteriorly. No diverticula were demonstrated in the remainder of the gastro-intestinal tract.

CASE II. MILD SYMPTOMS AND GROSS HEMORRHAGE.—The patient, a forty-four-year-old man, experienced a sensation of heaviness beneath the lower sternum, and, unassociated with nausea, retching or pain, vomited a cupful of bright red blood two hours following the midday meal. Immediately he felt well except for a soreness beneath the midsternum on eating. Symptoms persisted for only a few days. Laboratory examination

was directed to the left anteriorly, and in one third to the right anteriorly. In most of the cases there was a single sac.

Considerable variation existed in shape and capacity of the sacs, and no relationship existed between size and the causation of symptoms. Some of the smaller sacs caused the most severe symptoms while the largest was entirely silent. All of the diverticula were seen to contract, and emptied the entire contents while under observation.
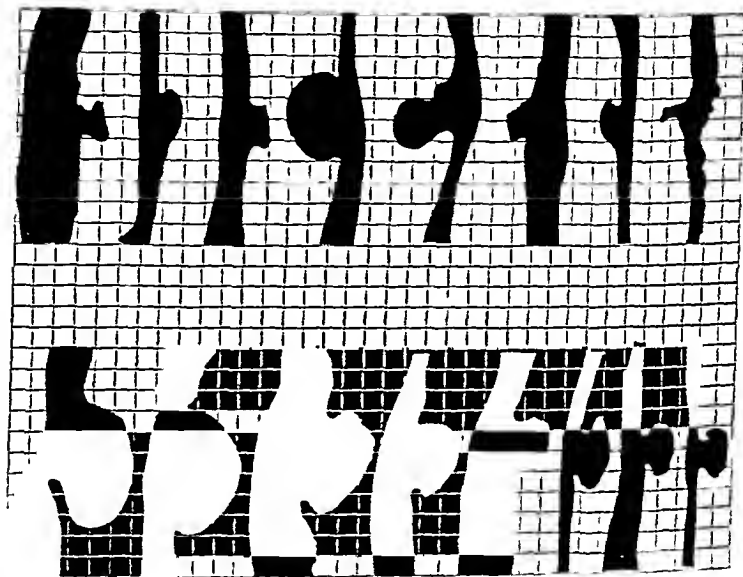
Fig. 147.—Exact patterns of the diverticula projected from the roentgenograms onto centimetergraph paper. Target-film distance 30 inches (75 cm.).

Fluoroscopic examination constitutes the diagnostic method of choice. The ability to visualize the esophagus in all planes while under direct observation, due to rotation of the patient. insures positioning the sac squarely in the silhouette. A vertical position, and not the horizontal, offers the advantage that strong peristalsis is not excited in transport of the opaque bolus down the esophagus. Peristalsis obliterates the sac opening and prevents filling. Even with the vertical position, the main portion of the mixture passes the diverticulum opening

before esophageal tonus is sufficiently relaxed for the barium to enter the sac, and filling seems to occur by back pressure.

The importance of employing a *proper contrast medium* cannot be overemphasized. A proprietary opaque medium, Rugar, after conscientious trial, has not given such consistently satisfactory results as a freshly prepared barium-mucilage of acacia mixture. By means of a metal spoon and a stout cup the mucilage is vigorously mixed with powdered barium until a homogeneous semiliquid is obtained. The desired consistency may show considerable variation with the preference of the examiner. A mixture thin enough to flow in a slow, continuous, sticky stream results in better visualization than one which drops from the spoon in chunks. The correct medium produces a dense shadow, necessitates 1 teaspoonful for examination of the entire esophagus in each plane and is swallowed piecemeal.

In order to demonstrate the type and severity of the symptoms customarily encountered, four of the forty cases are presented:

ILLUSTRATIVE CASES

CASE I. MILD SYMPTOMS.—The patient is a forty-five-year-old man, who was formerly an habitual and excessive drinker of whiskey. Suspecting this to be the cause of his illness he abstained from drinking but without relief. There had been eight or more admissions to other hospitals for attacks of a burning sensation in the upper abdomen, hiccough, and a heaviness in the left chest. The chest pain was vague, occasionally substernal, and at rare times was aggravated by eating. The only clinical findings were three small diverticula, one above the other, located in the midthird of the esophagus with the long axes directed to the left anteriorly. No diverticula were demonstrated in the remainder of the gastro-intestinal tract.

CASE II. MILD SYMPTOMS AND GROSS HEMORRHAGE.—The patient, a forty-four-year-old man, experienced a sensation of heaviness beneath the lower sternum, and, unassociated with nausea, retching or pain, vomited a cupful of bright red blood two hours following the midday meal. Immediately he felt well except for a soreness beneath the midsternum on eating. Symptoms persisted for only a few days. Laboratory examination

showed no anemia. Blood pressure in mm. of mercury was 110 systolic, 70 diastolic. Urine, gastric analysis, stool and Wassermann test were negative. A gastro-intestinal x-ray series showed no ulcer. Fluoroscopic examination of the esophagus revealed a small diverticulum located in the mid-third of the esophagus, the long axis directed to the right anteriorly.

CASE III. MODERATELY SEVERE SYMPTOMS.—The patient, a woman sixty-six years old, developed a pulsion diverticulum, pointing to the right side at the base of the neck. At operation the sac was ligated and fixed high up beneath the neck muscles, changing the axis of the sac to from above and down. She remained well for one year, at which time symptoms recurred. X-ray examination showed the pulsion diverticulum re-established, somewhat enlarged and assuming the original position. About two years postoperatively she complained of sharp substernal pain of short duration in addition to a dull, constant heaviness felt behind the midsternum and also in the back. Pain was at times burning in character. There was no dysphagia. The symptoms have persisted, and have been present on the numerous occasions in the past three years that she has visited the clinic. Fluoroscopic examination of the esophagus revealed a single diverticulum ¼ inch wide by ¾ inch long, having a pointed tip with the axis directed slightly downward.

CASE IV. SYMPTOMS OF EXTREME SEVERITY.—The patient, a woman, first noticed at the age of forty, in 1926, pain behind the sternum and difficulty in swallowing solids. The symptoms gradually became extreme, and at the end of three years she had curtailed the diet to liquids and soft foods. She was admitted to the Ear, Nose and Throat Ward where direct esophagoscopic examination failed to show abnormality or obstruction. No fluoroscopic or roentgenographic examination was performed. The diagnosis on discharge was esophageal spasm, and the examination had apparently relieved all her symptoms.

During the succeeding four years comfort was complete. The diet was general, and consisted of all foods brought to the family table. However, at the end of this time, 1930, the original symptoms recurred in equal severity and the patient was admitted to the medical ward. Roentgen examination of the esophagus showed no abnormality, but the fluoroscopic examination revealed a single, small traction diverticulum of the mid-third of the esophagus directed to the right laterally. Treatment con-

sisted of soft diet, morphine and atropine for the severe pain, and the patient gradually improved.

Except for an occasional mild discomfort she remained well for two years. In 1932, when the third attack necessitated hospitalization, the symptoms were more severe than ever before. Fluoroscopic examination visualized the single diverticulum unchanged.

The fourth attack, 1933, was mild and of short duration. The pain was associated with regurgitation, but no vomiting. The diverticulum was visible on both fluoroscopic and roentgen examinations, and a moderate degree of esophageal spasm was present.

The fifth attack, 1939, after six years of comfort, recurred in the most severe form. Pain was intense and required frequent narcotics. She refused to eat or drink, became dehydrated and her fever began to rise. Dilatation of the esophagus with a mercury bougie and stretching of the cardia with a mercury pneumatic dilator were performed, but no benefit resulted. Starvation and dehydration became so extreme that a gastrostomy was performed for feeding. At the end of three months there was no discomfort, there had been a substantial gain in weight, and the gastrostomy opening was closed.

On December 1, 1941, the patient is entirely well after five distinct acute attacks and numerous short periods of mild discomfort during the past sixteen years.

TREATMENT

The treatment of traction diverticulum of the esophagus has proved, in all respects, entirely unsatisfactory. The location, deep in the thoracic cavity, and in close proximity to vital structures, has prevented the employment of surgical treatment. The drugs that have been used for symptomatic relief produce only partial comfort, and are required in full dosage. On the principle that coarse foods may be irritating, and that harsh indigestible fibers and brans may be incarcerated in the sac, a *smooth diet* is recommended. *Demulcent preparations* are prescribed and *lubricants*, such as petrolatum, liquid petrolatum and olive oil, are given on an empirical basis. The *mild sedatives*, as the bromides, chloral hydrate and the barbituric acid derivatives, assist in inducing sleep but do not relieve the pain. *Antispasmodic drugs* are admin-

istered in full dosage up to the point of tolerance without resulting in permanent or definite relief. Analgesic drugs are of no benefit.

Morphine given in heavy dosage relieves temporarily while the effect is strong. *Cocaine,* 0.06 gm. dissolved in 32 cc. of a liquid vehicle, and administered by a nurse in 4 cc. amounts when the pain becomes intense, has given more relief than any other remedy employed. In addition, the mild stimulation and excitation produced is a pleasant relief from the suffering. The dangers inherent with such a remedy if possible are to be avoided. A 2 per cent pontocaine solution proved ineffectual when swallowed. Short wave diathermy and roentgen therapy has not caused cessation of the pain.

Dilatation of the esophagus and dilatation of the cardia, one or more times, has been followed by some relief of symptoms. This procedure has been accomplished with olive-tipped rigid bougies applied under observation through the esophagoscope. The plain mercury bougie can be easily and frequently employed, the patient instructed in the passage for self-treatment at home. The combined mercury-pneumatic bougie and dilator, an easy safe instrument to pass, produces the best results from instrumentation. When the dilator part is employed, the pressure used is limited by the pain induced —usually not above 2 or 3 pounds. With higher pressures the esophagus may not only be dilated but avulsed.

LABORATORY AIDS IN GASTRO-INTESTINAL DISORDERS*

NATHAN W. CHAIKIN, M.D.†

and

LINDSLEY F. COCHEU, M.D.‡

In attempting to arrive at a diagnosis in diseases of the gastro-intestinal tract, one must correlate the clinical picture with laboratory data. Such laboratory data should be all-inclusive, with reference not only to the system under investigation but even to those systems indirectly involved.

In the investigation of diseases of the alimentary tract, laboratory data of paramount importance are radiographic examination, secretory status of the stomach, functional status of the hepatobiliary system (which should include duodenal drainage), various liver function tests, and examination of feces. No examination of the gastro-intestinal system is complete without investigation of the hemopoietic system and the chemical constituents of blood.

SECRETORY STATUS OF STOMACH

With all the criticism that the gastric test meal has been subjected to, both physiologically and analytically, it still is, by and large, the only available means of estimating the secretory status of the gastric mucosa. Physiologically, there are a great many variations in perfectly normal, healthy individuals, extending from complete anacidity to a marked hyperacidity. Allowing for variations of age, sex and psychoneurosis, the gastric analysis is still of utmost importance in

* From the Departments of Medicine and Clinical Pathology (Metropolitan Hospital Service), New York Medical College.
† Clinical Instructor in Medicine (Gastro-enterology), New York Medical College, Flower and Fifth Avenue Hospitals; Associate Visiting Physician, Metropolitan Hospital.
‡ Professor of Bacteriology, Clinical Pathology and Public Health, New York Medical College, Flower and Fifth Avenue Hospitals; Consulting Pathologist, Metropolitan Hospital.

istered in full dosage up to the point of tolerance without resulting in permanent or definite relief. Analgesic drugs are of no benefit.

Morphine given in heavy dosage relieves temporarily while the effect is strong. *Cocaine*, 0.06 gm. dissolved in 32 cc. of a liquid vehicle, and administered by a nurse in 4 cc. amounts when the pain becomes intense, has given more relief than any other remedy employed. In addition, the mild stimulation and excitation produced is a pleasant relief from the suffering. The dangers inherent with such a remedy if possible are to be avoided. A 2 per cent pontocaine solution proved ineffectual when swallowed. Short wave diathermy and roentgen therapy has not caused cessation of the pain.

Dilatation of the esophagus and dilatation of the cardia, one or more times, has been followed by some relief of symptoms. This procedure has been accomplished with olive-tipped rigid bougies applied under observation through the esophagoscope. The plain mercury bougie can be easily and frequently employed, the patient instructed in the passage for self-treatment at home. The combined mercury-pneumatic bougie and dilator, an easy safe instrument to pass, produces the best results from instrumentation. When the dilator part is employed, the pressure used is limited by the pain induced —usually not above 2 or 3 pounds. With higher pressures the esophagus may not only be dilated but avulsed.

lined the following criteria as essential in the ideal test meal: The test must be applied under standard conditions; the stimulus or work which constitutes the test must impose a load on the functions to be tested, and the test should be capable of yielding similar results on repetition. From our own experience, we have found that the use of the histamine test as outlined by these observers is the most valuable.

While the Ewald test is still popular for routine purposes, it is not a true index of the secretory power of the gastric mucosa or a true quantitative index of the acid findings, and it has, therefore, been replaced by either alcohol or histamine stimulation. Where vagotomy has been employed in the surgical procedures, the insulin test is used to determine the extent of its exclusion.

ANEMIA IN RELATION TO GASTRO-INTESTINAL DISORDERS

Hypochromic Anemia

There is no longer any doubt that disorders of the gastrointestinal tract play a part in a large percentage of the cases of hypochromic anemia and may even be one of the chief etiologic factors in such anemias. This is especially prominent in gastro-intestinal lesions accompanied by hypoacidity, or anacidity in which the anemias have been ascribed by many workers to the accompanying disturbances in the absorptive power of the alimentary canal. Certainly, such changes are a frequent finding in many types of hypochromic anemia. Thus, Wintrobe and Beebe found more than 50 per cent of their patients with idiopathic hypochromic anemia unable to secrete hydrochloric acid after histamine injection and found normal secretion in less than 10 per cent of their patients; their findings were confirmed by Domashed, Castle and Minot.

Other students of the subject have found significant depressions in gastric secretion in the hypochromic anemias of pregnancy and in hookworm disease, and in the secondary anemias associated with dietary deficiencies and dysentery. Metter and Minot, in an attempt to explain the relationship between hypochromic anemia and gastric anacidity, have shown that idiopathic hypochromic anemia is accompanied

pathologic states. In evaluating the data obtained from gastric analysis, one must bear in mind that there are no exclusive findings in any pathological condition, and the subject resolves itself into a matter of frequencies. Despite the overlapping values, some differentiation is possible.

Experience has shown us that, as a rule (subject to exceptions), most patients with ulcer have high acidity and high volume, while the opposite is true in carcinoma and pernicious anemia. In the so-called *dyspepsias*, hypoacidity occurs with somewhat greater frequency than hyperacidity. Such hypoacidity characterizes more particularly the functional gastric disturbances accompanying infections, intoxications, diabetes, nephritis and endocrine disorders. *Neuroses* of the hyperasthenic type are generally marked by increased gastro-intestinal motility and hypersecretion; those of the hyposthenic type by depressed motor and secretory activity.

In *acute gastritis* in which the examination is ordinarily limited to the vomitus, which contains besides food residue, mucus, bile, and at times, blood, the hydrochloric acid is neutralized, and consequently no free hydrochloric acid is found. In *chronic gastritis*, hypersecretion and hyperacidity may be prominent at first, but eventually the secretion becomes scanty and is composed largely of viscid mucus. There is no free acid, and the total titrable acid is disproportionately high because of large amounts of mucin which combines with either acid or base.

Hyperacidity is encountered more frequently in duodenal than in gastric ulcers. In a group of *duodenal ulcer* cases reported by a number of investigators, the concentration of free hydrochloric acid ranged from 20 to 115 units, whereas in a group of gastric ulcer cases, the range was from 25 to 95 units. So great can the variation be that in a considerable number of ulcer cases the concentration of acid may fall between normal limits. This is especially true of gastric ulcer.

In *carcinoma of the stomach*, anacidity or low acidity and low volume are usually found. The maximum ten-minute volume does not exceed 15 cc., and secretion is mostly mucus. However, in a number of cases, normal gastric acidity is encountered.

Criteria for Test Meal.—Bloomfield and Polland have out-

lined the following criteria as essential in the ideal test meal: The test must be applied under standard conditions; the stimulus or work which constitutes the test must impose a load on the functions to be tested, and the test should be capable of yielding similar results on repetition. From our own experience, we have found that the use of the histamine test as outlined by these observers is the most valuable.

While the Ewald test is still popular for routine purposes, it is not a true index of the secretory power of the gastric mucosa or a true quantitative index of the acid findings, and it has, therefore, been replaced by either alcohol or histamine stimulation. Where vagotomy has been employed in the surgical procedures, the insulin test is used to determine the extent of its exclusion.

ANEMIA IN RELATION TO GASTRO-INTESTINAL DISORDERS

Hypochromic Anemia

There is no longer any doubt that disorders of the gastro-intestinal tract play a part in a large percentage of the cases of hypochromic anemia and may even be one of the chief etiologic factors in such anemias. This is especially prominent in gastro-intestinal lesions accompanied by hypoacidity, or anacidity in which the anemias have been ascribed by many workers to the accompanying disturbances in the absorptive power of the alimentary canal. Certainly, such changes are a frequent finding in many types of hypochromic anemia. Thus, Wintrobe and Beebe found more than 50 per cent of their patients with idiopathic hypochromic anemia unable to secrete hydrochloric acid after histamine injection and found normal secretion in less than 10 per cent of their patients; their findings were confirmed by Domashed, Castle and Minot.

Other students of the subject have found significant depressions in gastric secretion in the hypochromic anemias of pregnancy and in hookworm disease, and in the secondary anemias associated with dietary deficiencies and dysentery. Metter and Minot, in an attempt to explain the relationship between hypochromic anemia and gastric anacidity, have shown that idiopathic hypochromic anemia is accompanied

by greater response of the bone marrow to iron, when the upper intestinal tract is rendered more acid. The factor of faulty absorption has also been advanced, as is indicated by the work of Lind and E. Weschler. They showed that galactose is poorly absorbed from the intestinal tracts of patients with gastric anacidity in idiopathic hypochromic anemia. The relationship of *diarrhea* to hypochromic anemia has likewise been explained on the basis of faulty absorption of iron due to the excessively rapid passage of the intestinal contents. It is thus apparent that gastro-intestinal pathologic change remains one of the chief causes for the development of the hypochromic anemias.

Of great interest is the profound hypochromic anemia which occurs in the presence of *neoplastic lesions of the colon*, especially of the cecum and the ascending colon. The extreme low color index, 0.5, appears to be out of proportion to any hemorrhage that may be taking place. Excessive mucin may inhibit or delay absorption of iron. Thus, in the absence of bleeding, which is the most common cause of secondary anemia in lesions in the gastro-intestinal tract, the close relationship between hypochromic anemias and the status of the gastric mucosa is evident.

Macrocytic Anemias

The past decade has seen an almost revolutionary development in our conception of the tie-up between the macrocytic anemias and the gastro-intestinal tract, the mechanism of which may be: (1) insufficient extrinsic factor because of ill-advised or unavoidable dietary restriction; (2) lack of intrinsic factor, such as must follow gastrectomy and other operative procedures on the gastro-intestinal tract; (3) impaired intestinal absorption. The conditions in which this type of anemia is commonly encountered are total or partial gastrectomy, gastro-enterostomy, entero-enterostomy, gastric carcinoma, prolonged diarrhea of amebic or bacillary dysentery, ulcerative colitis, idiopathic steatorrhea, and in certain disease of the liver. The macrocytic type of anemia associated with hepatic cirrhosis, or where there is extensive liver damage, is explained by the inability of the diseased liver to store, synthesize, or release the hematopoietic material. In

view of the above, the importance of a proper evaluation of blood findings assumes great proportion.

HEPATOBILIARY SYSTEM

The laboratory aspect in diseases of the hepatobiliary system has proved to be of such inestimable practical help that no clinical diagnosis should be made unless supplemented by the various procedures. These should be aimed at determining the patency of the biliary tree, pancreatic function when possible, and the integrity of the liver parenchyma.

Duodenal Drainage.—In the procedure of duodenal drainage, as advocated by Lyons and other investigators, one can determine the patency of the biliary tree and the state of the gallbladder, and it is a means, although with great limitations, of studying the pancreatic enzymes.

In complete obstruction of the common bile duct, bile will not be found in the duodenal contents, and the presence of gross blood may constitute a strong argument for the presence of neoplastic biliary obstruction and in some cases, of calculus obstruction. Where such obstruction is complete, the response to stimulation with magnesium sulfate does not take place. When, on the other hand, the obstruction is of a temporary nature, such as spasm of the sphincter of Oddi or intraductal inflammatory edema, the response to stimulation may be delayed for hours. In the microscopic examination, the presence of cholesterol and bilirubin-calcium crystals is pathognomonic of cholelithiasis.

Study of Pancreatic Enzymes.—Biliary disease is so frequently associated with pancreatic disturbances that a study of pancreatic enzymes should be attempted wherever possible.

In recent years the technic of pancreatic enzyme study has been improved, but in spite of this refinement the methods still have their limitations. They can be criticized on both physiological and analytical grounds. The obvious shortcoming in this procedure is the difficulty of obtaining a pure sample of pancreatic juice without contamination and dilution with gastric and duodenal contents. Furthermore, there are no available means of an absolutely accurate determination of pancreatic enzymes which would give one a constantly reproducible result. By means of secretin and the use of a

bilumen tube, the factor of dilution and contamination has been partially overcome.

The response of the pancreas to intravenous injection of secretin is an increase to the volume of flow of pancreatic juice, increased concentration and quantity of the enzymes, diastase, trypsin and lipase, and also an increase in the concentration of bicarbonates above basal levels.

The methods employed for the determination of enzymes are as follows:

Diastase: Norby's method modified for duodenal contents.
Trypsin: Willstatter's method.
Lipase: The method of Cherry and Crandall modified by Comfort and Osterberg, using a 1:10 dilution.

In pathologic states, there is a marked reduction in any of the above factors (namely volume, diastase, trypsin, lipase and bicarbonate concentration). The importance of enzyme reduction is not so much of all three enzymes, but rather a so-called dissociation in which lipase and trypsin activity is usually most affected and diastase the least. At present the secretin response test is of primary value in differentiating between obstructive phenomena in the ductal system and pancreatic deficiencies. In complete obstruction of the common duct such as occurs in impaction of stones in the ampulla of Vater, or tumors involving both ducts, the simultaneous absence of bile and pancreatic juice points to a surgical type of obstruction. When the pancreas is primarily involved, as in common pancreatitis and tumor, a reduction in the activity in any one of the enzymes is observed. Further studies of this test may elucidate many problems of pancreatic disturbances.

LIVER FUNCTIONS

Because of the diverse functions of the liver, no one functional test is of absolute diagnostic value, and all are of a contributory nature. It is the clinical picture which should be of paramount importance, and too much reliance should not be placed on the significance of any individual test.

The *bromsulfthalein,* the *bilirubin* and *rose bengal tests,* which are based on the excretory function of the liver, consist of intravenous injection of the respective materials, and

the rate of excretion is estimated from the quantity retained in the serum after the lapse of a specified time. The concentration of the material in the serum is determined colorimetrically. These substances are excreted practically entirely by the liver, and no significant amounts are taken up by reticulo-endothelial cells.

Because of the availability of other tests whereby the integrity of the liver can be ascertained, the rationale of using these tests is questionable, for an additional load is imposed upon the excretory function of the liver.

Van den Bergh Reaction.—The interpretation of the Van den Bergh reaction should be made with certain reservations. While it is true that the direct reacting or indirect reacting bilirubin is due to the passage or nonpassage of the bilirubin through the polygonal cells, yet the fact remains that all types of reactions may occur in non-hemolytic icterus during various stages of jaundice. It would seem, according to Bockus, that it is the amount of bilirubin present in the serum which may be the determining factor in the type of Van den Bergh reaction obtained. The greater the amount of bilirubin in the serum, the more likely is the possibility of a direct reaction regardless of the cause.

As a rule, however, an *immediate* Van den Bergh is indicative of the fact that the protein molecule has been dissociated from the bilirubin, and, therefore, the bilirubin must have passed through the cells of the liver and been resorbed or regurgitated into the blood stream, implying an obstructive type of jaundice.

The so-called *biphasic* Van den Bergh, which is encountered in liver damage, is generally accounted for by the presence of large amounts of normal serum bilirubin on one hand, and a considerable amount of dissociated bilirubin on the other.

In the light of our own experience, we have found that the proper evaluation of cholesterol partition, cephalin-cholesterol flocculation, the albumin-globulin ratio, synthesis of hippuric acid and sugar tolerance give sufficient data to determine the presence or absence and the extent of liver damage.

Cholesterol and Cholesterol Ester Fraction.—There is sufficient ground to believe that the liver is concerned with

cholesterol metabolism, and that esterification of cholesterol goes on in the liver. In patients with liver damage, the cholesterol-ester fraction is reduced in proportion to the extent of liver damage. Not only does it express involvement of the liver, but it is also of definite prognostic value in preoperative and postoperative biliary surgery. Normally, the blood cholesterol is between 140 and 220; the ester fraction of which is between 50 and 60 per cent. If the ester fraction is less than 40 per cent of the total cholesterols, it is inevitably associated with liver damage, a finding which is corroborated by other liver function tests and clinical picture.

Cephalin-cholesterol Flocculation Test.—This test as introduced by Hangar is based upon the fact that in patients with active liver damage the blood serum possesses the quality of flocculating a cephalin-cholesterol emulsion, whereas sera of normal subjects uniformly produce no flocculation. Its value has been definitely established, and it is at present being routinely used on our service.

Albumin-globulin Ratio.—In cases of liver involvement, the total plasma protein is decreased and particularly the albumin fraction. The albumin-globulin ratio frequently approaches 1:1. Other conditions in which this ratio is disturbed must be ruled out, such as nephrosis, severe alkalosis and occasional cases of hyperthyroidism. The exact mechanism in the disturbance of the protein molecule is not very well understood. When ascites is present, the loss of albumin from the ascitic fluid or the increased capillary permeability allowing the escape of protein into the tissues may be a primary factor. On the other hand, an injured liver may be deficient in handling protein-building substances resulting in a decreased level of serum protein. Lowered serum protein levels are not only encountered in liver disease but also in severe cases of gastro-intestinal hemorrhage. In extensive gastro-intestinal hemorrhage, the total serum protein may be as low as 4 or 5, and it is reasonable to assume that the beneficial results obtained by the Meulengracht diet in such cases are probably due to a more rapid replacement of the plasma proteins.

Hippuric Acid Test.—The detoxifying action of the liver is studied by the hippuric acid test as devised by Quick. It is based on the ability of the liver to effect synthesis of ben-

zoic acid and glycine and to eliminate it in the form of hippuric acid. The test should be limited to cases in which the amount of urea is within normal limits. The total hippuric acid eliminated from the liver with some reserve is 3.6 gm. When the excretion of hippuric acid is 1.5 gm. or less, a severely damaged liver is probably present. It should be used as a guide in surgical procedures on the biliary tract. The surgical risk is definitely increased in the presence of low excretion of hippuric acid. Because the test is readily affected by renal insufficiency, it should be done simultaneously with the urea clearance; rather it should be used as an index of hepatic insufficiency than as a differential. This test has been recently modified by Quick and his associates. To obviate the disadvantages of the oral administration of sodium benzoate, the intravenous route is now being used. During the first hour following injection of 1.5 gm. of benzoic acid, 0.7–0.95 gm. is excreted as hippuric acid by normal adults. It has been conclusively proved to be a very sensitive test of liver dysfunction, and great reliance should be placed on it when surgical intervention is contemplated in the presence of liver damage.

Galactose Tolerance and Levulose Tolerance.—The galactose tolerance test is the most widely used single test employed in differentiating between extrahepatic and intrahepatic jaundice. It is based upon the fact that a normally functioning liver can utilize a dose of 40 gm. of galactose without producing any change in the level of the blood sugar, and therefore no significant glycosuria follows. Recently the intravenous method has been used, consisting of injecting 100 cc. of properly warmed, sterilized, and buffered solution of galactose. Patients with normal livers will show complete utilization of 25 gm. of galactose within one hour. The levulose tolerance test is occasionally used, and normally the blood sugar is not affected by the oral administration of levulose, but it is increased in hepatic disease.

Phosphatase.—Phosphatase, which is normally present in the blood serum and the bile, may be increased in biliary obstruction either because of obstruction of the biliary flow or of regurgitation into the blood of phosphatase in the bile.

Vitamin K Therapeutic Test.—The integrity of the liver is

now also being judged by its ability to respond to therapeutic doses of synthetic vitamin K. In the presence of low prothrombin levels, a normal liver will respond to a therapeutic dose of synthetic vitamin K by an increase of 10 to 15 per cent within twenty-four to seventy-two hours. Such increase does not take place in the presence of liver damage.

GASTRO-INTESTINAL OBSTRUCTIONS

As diagnostic aids in obstructive lesions of the gastrointestinal tract, the determination of the electrolytes in the blood and plain roentgenograms of the abdomen without the use of contrast media constitute the most important adjuncts to the clinical picture.

Nitrogen Bodies in the Blood.—In pyloric or high intestinal obstruction, secretion of large quantities of gastric juice entails a loss of blood chlorides. The chloride depletion is associated with retention of carbon dioxide, and as a consequence of this, an increase in the bicarbonate. This compensatory mechanism leads to alkalosis and dehydration. Dehydration also brings about increased tissue destruction and decreased kidney function. It is this combination of circumstances which leads to marked increase in concentration of the nonprotein nitrogenous constituents of the blood. Another view for which there is little or no direct evidence is that renal damage in intestinal obstruction is due to some circulating toxin. Restoration to normal occurs after the obstruction is relieved.

Azotemia is encountered not only in gastro-intestinal obstruction, but also in extensive hemorrhages from the gastrointestinal tract. The mechanism of azotemia in gastrointestinal hemorrhage has been investigated by numerous observers who expounded widely different views as to its production. From the clinical point of view and recent experimental findings presented, it would appear that the mechanism of alimentary azotemia is due to the absorption of the digestion products of whole blood in the gastro-intestinal tract. Renal impairment, hypochloremia, and hemoconcentration play no role in the production of this type of azotemia. From our own observation, we can state that the

azotemia has a direct relationship to the severity of the hemorrhage. In a number of our cases, where the urea nitrogen was persistently high, a stormy clinical course was encountered. However, we had no fatalities in our azotemic group. One may conclude that persistent azotemia is indicative of repeated hemorrhages as evidenced by further hematemesis and melena. The azotemia in hemorrhages thus depends upon the extent of the hemorrhage and also upon the time interval in which the blood is examined.

In obstruction, there is first a fair degree of adjustment in the blood to the loss of chloride, acid ions, base and water, but with failure of the compensatory mechanism occasioned by the continued depletion of the extracellular fluid, the changes in the blood become rapidly progressive. These manifest themselves by reduction in the chlorides, rise of carbon dioxide combining power, alkalosis. even though the total plasma base is diminished, and increased nonprotein nitrogen—changes which are illustrated in the case following.

Roentgenologic Studies.—While it is not within our province to discuss roentgenological findings, their obvious significance in the diagnosis of obstructive lesions deserves mention.

The plain roentgenogram of the abdomen without the use of contrast media helps to differentiate between large and small bowel obstructions. It may save surgical intervention in patients with signs suggestive of ileus and in a rough fashion it may help to localize obstruction of the colon.

EXAMINATION OF FECES

The examination of feces constitutes an important link in the investigation of pathologic states of the alimentary tract. It offers a means of differentiation of the various types of steatorrheas encountered in clinical medicine as well as the differentiation of amebic dysentery from various forms of bacillary dysentery and inflammatory conditions of the large bowel causing diarrheas.

In the *steatorrheas*, it is the determination of total fats, neutral fats. free fatty acids, the nitrogen, as well as the presence or absence in the stool of undigested muscle fibers,

which helps one to differentiate pancreatic deficiencies from sprue or idiopathic steatorrheas, since deficiencies of nitrogen absorption with predominance of neutral fat are characteristic of pancreatic deficiency.

The differentiation of the various *diarrheas* is facilitated by the study of the cellular exudate. In diarrheas of pyogenic origin as well as those of the bacillary group, pus cells are invariably found in the stool, which is contrary to that of amebic dysentery. Toxic degeneration of the nuclei in the pus cells, pyknotic bodies, Charcot-Leyden crystals, and macrophages are additional points of differentiation.

The presence of *occult blood* in the stool should be interpreted with caution. It does not convey the localization nor the nature of the lesion. Its presence may be due to lesions outside the gastro-intestinal tract, such as gingivitis, inflammation of the nose and throat, or to ulcerative lesions of either benign or malignant nature extending from the esophagus to and including the large bowel. It may also suggest polycythemias and other types of hemorrhagic diastheses.

The absence of *urobilinogen* from the stools is found in the obstruction of the common duct, which may be due either to a neoplasm or a stone, and frequently in hepatitis or cholangitis.

EXAMINATION OF THE URINE

Bile in the urine is, of course, indicative of obstruction somewhere between the liver cells and the ampulla of Vater. *Urobilin*, on the other hand, usually means damaged liver cells, but it is commonly increased when obstruction is present. Even if obstruction is complete, urobilin will be recovered in the urine in the presence of infected biliary ways.

CONCLUSION

Examinations of the contents of the intestinal tract have their place, and at times give information which could not be obtained by other means. On the other hand, other types of laboratory investigations are frequently called for if one is to derive all of the benefit which may be obtained. An attempt has been made to indicate some of the more important laboratory aids in gastro-intestinal disorders.

CORONARY INSUFFICIENCY

ERNST P. BOAS, M.D.*

ALL cardiac symptoms resulting from disease of the coronary arteries are in fact due to coronary insufficiency. Symptoms arise when for any reason the blood flow through the coronary arteries is insufficient to meet the immediate metabolic needs of the heart muscle. A relative anoxemia results and this induces cardiac pain. Attacks of uncomplicated angina pectoris are due to myocardial anoxemia. In the presence of coronary artery sclerosis the coronary arteries give passage to sufficient blood flow when the patient is not overtaxing himself, but when effort, eating or excitement increases the work of the heart, the narrowed coronary arteries do not permit an adequate compensatory blood flow to reach the myocardium, and pain results. In many instances objective evidence of this myocardial ischemia can be obtained by taking an electrocardiogram during an attack of angina pectoris. Depression of the RT or ST segment may be present and disappears in a short time with recovery from the attack of pain.

For clinical purposes we do not designate simple angina pectoris as coronary insufficiency, although such insufficiency underlies the mechanism of the attack. Coronary occlusion resulting in cardiac infarction represents an extreme form of coronary insufficiency. Myocardial anoxemia is so complete and prolonged that infarction of the heart muscle results. Again, clinically we do not classify these cases among the group of coronary insufficiency.

MECHANISMS OF INDUCTION

Coronary insufficiency is encountered most often in patients with coronary arteriosclerosis, and may be induced by

* Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University; Associate Physician, Mt. Sinai Hospital.

several mechanisms. *Physical effort* or great *emotional strain* may whip up the circulation to such a degree that the narrowed coronary arterial bed cannot accommodate the needed compensatory flow of blood to the overworking myocardium. Myocardial anoxemia with resulting pain ensues. This pain may be severe and prolonged. *Paroxysmal tachycardia* or *auricular fibrillation* may in a similar way increase the need of the heart muscle for blood, a need that cannot be met by the narrowed arterial bed. *Shock* or *hemorrhage* induce coronary insufficiency in a different manner. Shock or hemorrhage is followed by a marked drop in blood pressure and in blood flow, and this in turn, in the presence of narrowed coronary arteries leads to coronary insufficiency. Commonly the interference with coronary flow is sufficient to cause cardiac infarction. *Airplane flights* to high altitudes where the partial pressure of oxygen is low may in persons with coronary artery disease lead to coronary insufficiency, and severe anginal seizures. In at least one reported case death resulted. *Severe anemia*, in the presence of coronary arteriosclerosis, may similarly lead to myocardial anoxemia and coronary insufficiency.

At times coronary insufficiency may be manifest in the absence of all of these factors. In the absence of unusual physical or emotional strain, or of abnormal heart rhythms, in the absence of hemorrhage or shock, and without exposure to low atmospheric pressures a patient with coronary artery disease may experience repeated anginal attacks at rest, and without apparent cause. In such cases the degree of narrowing of at least one of the coronary arteries is so far advanced that the blood may be said to pass through it in a mere trickle. The slightest alteration of the circulation in response to the normal physiologic functioning of the body retards or halts this precarious flow of blood, and the anginal pain of coronary insufficiency results.

CARDIAC INFARCTION

No matter which of these mechanisms is at play, the symptoms are much the same. If the insufficiency of the coronary circulation is short-lived no permanent injury to heart mus-

cle or cardiac function results, but if it persists for half an hour or more necrosis of the heart muscle fibers occurs, and a cardiac infarct may form. Thus, coronary insufficiency without coronary occlusion may induce cardiac infarction. On the other hand, coronary thrombosis may take place without resulting cardiac infarction, if the collateral circulation of the affected portion of the heart muscle is adequate.

The differential diagnosis between coronary thrombosis and coronary insufficiency often can be made only on the autopsy table. But it is always possible to recognize whether or not *infarction* of the heart muscle has taken place. When a person experiences a sudden severe anginal attack when he is at complete rest, and without apparent cause, one may assume that a coronary thrombosis has occurred. When, in the days following, fever, leukocytosis and an acceleration of the sedimentation rate of the red blood cells occur, and the electrocardiogram shows characteristic changes one knows that a cardiac infarction has followed the thrombosis. But if all of these signs remain absent, one can assume that a coronary thrombosis without cardiac infarction has taken place. On the other hand, if a prolonged anginal seizure follows severe effort it is quite possible that it has resulted from insufficiency of sclerotic coronary arteries, and if the symptoms of cardiac infarction follow, such myocardial injury may have resulted without closure of a coronary artery.

CASES ILLUSTRATING CORONARY INSUFFICIENCY

Case I. Coronary Insufficiency without Cardiac Infarction Induced by Effort

A man, aged forty-five years, for some months had noted that running to catch a bus, or walking briskly up hill would induce substernal oppression that compelled him to slow his pace. One morning he was late to work, and seeing an elevated train coming dashed up the stairs to catch it. As he reached the train he was seized with agonizing substernal pain that radiated down the left arm, and was hardly able to draw a breath. He felt cold, and broke into a sweat. He slumped in a seat, but managed to drag himself out of the train at the next station, and took a taxi to his home. The pain lasted about forty-five minutes, but it took about two days for him to come back to himself. Examina-

tion on the days following this incident revealed no change in his cardiac status, the electrocardiogram was normal, there was no fever and there were no abnormal blood findings.

Case II. Coronary Insufficiency Followed by Cardiac Infarction Induced by Severe Emotional Disturbance

A man, aged fifty-four years, had had mild diabetes for years, but no cardiac symptoms. One day he was called to the telephone and was told that his son who was at a tuberculosis sanatorium had suddenly died. Immediately he experienced agonizing substernal oppression and could hardly breathe. The pain gradually became milder but discomfort persisted for two days. One week later a second son died of Hodgkin's disease. Substernal pain followed by cough returned and he remained in bed for three weeks. Since that time he had typical anginal pain on walking. Examination two months later revealed great cardiac enlargement, feeble heart sounds, a blood pressure in mm. of mercury of 118 systolic and 80 diastolic, and an electrocardiographic pattern typical of infarction of the anterior aspect of the left ventricle.

Case III. Coronary Insufficiency without Cardiac Infarction Induced by Paroxysmal Auricular Fibrillation

A man, aged fifty-eight years, for some years had complained of substernal oppression on greater effort. He was careful not to overtax himself and continued at his work and did well. His heart was somewhat enlarged, the blood pressure was normal, and the electrocardiogram showed some slurring of the QRS which was widened to 0.12 seconds. Two days after an operation for the removal of a ureteral calculus he suddenly experienced severe palpitation, shortness of breath and sharp precordial and substernal pain. Examination revealed paroxysmal auricular fibrillation with a ventricular rate of 200. He received large doses of digitalis intravenously and by mouth, and within an hour the heart rate was reduced to 130, and two hours later normal sinus rhythm with a heart rate of 80 was restored. The substernal pain lasted until the ventricular rate dropped to 130. The clinical course during the following days showed that no cardiac infarction had taken place.

Case IV. Coronary Insufficiency without Cardiac Infarction Induced by Paroxysmal Tachycardia

A man, aged seventy-three years, who had a mild diabetes and a normal blood pressure had had no symptoms referable to his heart. One evening in May, 1938, while sitting quietly at home he suddenly experienced pressure across the upper chest which radiated to the back of the neck and to the head. He was not aware of palpitation but his physician noted a heart rate of 130. The patient received ½ grain of morphine and within a short time the pulse rate dropped to normal and the pain disappeared. I saw him three hours after the attack. He did not appear ill. The lungs were clear. The heart sounds were a bit faint. An electrocardiogram taken the following day was normal.

The patient felt quite well after this attack, was able to walk and experienced no anginal symptoms. Every few months he would have recurrent attacks similar to the first one in which his heart rate would jump to 130 or 140, and in which he would experience substernal pressure. An electrocardiogram was never taken during an attack, but they were evidently attacks of paroxysmal tachycardia or auricular flutter. It was soon found that 5 to 10 grains of quinidine sulfate would stop the attacks. In 1941 a suprapubic prostatectomy was done. While the patient was in the hospital he had several attacks of paroxysmal tachycardia, one of which lasted nine hours before it was relieved by quinidine sulfate. During the attacks he experienced substernal pressure and weakness of the left arm. Between attacks the patient feels quite well and his electrocardiogram remains normal.

This patient has coronary artery sclerosis, not sufficiently advanced to cause cardiac symptoms. When, however, he experiences an attack of paroxysmal tachycardia the increased work of the heart brings about an insufficiency of the coronary circulation. This patient illustrates coronary insufficiency arising in asymptomatic coronary arteriosclerosis as a result of paroxysmal rapid rhythm. In this instance the symptoms are mild. When the heart rate is more rapid, the attacks more prolonged, and the coronary disease more advanced, paroxysmal tachycardia may induce acute cardiac infarction as a result of prolonged and severe coronary insufficiency.

Case V. Coronary Insufficiency Due to Hyperthyroidism Complicating Coronary Artery Sclerosis

A woman, aged sixty-two years, had had a partial thyroidectomy for hyperthyroidism at thirty-four. At the age of fifty-seven she began to complain of exhaustion and mild retrosternal distress on walking eight blocks or so. Examination at that time revealed no evidences of hyperthyroidism. There was some enlargement of the left ventricle. The heart sounds were of good quality. Blood pressure in mm. of mercury was 165 systolic and 90 diastolic. The electrocardiogram was normal. Her symptoms gradually became aggravated and at the age of fifty-nine she was unable to walk more than a block because of sharp substernal pain and inability to breathe. At this time the heart had become larger. The blood pressure was unaltered, but the electrocardiogram revealed bundle branch block. Three months later she felt better and the electrocardiogram had returned to normal. The basal metabolic rate was + 11 per cent.

At the age of sixty, the patient began to be quite nervous, complained of palpitation and tremor of the hands. The pulse rate was 108. There was moderate firm enlargement of the thyroid gland and the basal metabolic rate was + 24 per cent. She was given small doses of Lugol's solution and gained some weight, but palpitation, tachycardia and nervousness persisted and the anginal symptoms remained very incapacitating. After a few months the bundle branch block recurred. In spite of careful medical treatment and prolonged bed rest the cardiac symptoms remained unchanged. Finally a subtotal thyroidectomy was performed. A large nodular goiter was removed. Following this her pulse slowed to 90 and although bundle branch block persisted her cardiac reserve improved greatly and she was able to be up and about and active without anginal symptoms.

Case VI. Coronary Insufficiency with Cardiac Infarction Induced by Severe Hemorrhage

A man, aged fifty-five years, had had symptoms typical of angina pectoris for one year. General physical examination was negative. The left ventricle and left auricle were enlarged. The heart sounds were of good quality. The blood pressure in mm. of mercury was 100 systolic and 60 diastolic. The electrocardiogram showed low T waves in the limb leads, and a deep Q wave in lead IV. His cardiac status remained unchanged for about a year, when he had a severe intestinal hemorrhage with collapse.

The hemoglobin dropped to 35 per cent. About two hours after the onset of the hemorrhage he was seized with intense substernal pain which lasted for hours and required morphine for relief. The electrocardiogram, on the following day, revealed a typical infarction of the posterior aspect of the left ventricle. The heart sounds were feeble, and he was febrile for ten days. He recovered from his cardiac infarction, and subsequently a carcinoma of the ascending colon was discovered for which he was successfully operated on.

Blumgart and his associates[1] have recently reported instances of multiple coronary thromboses following *shock*. All of the patients were elderly and had antecedent coronary disease. Among the conditions that induced the shock were diabetic coma, bleeding gastric ulcer, and pneumonia. In several cases shock following an initial coronary thrombosis led to subsequent multiple thromboses.

Benson[2] described the case of a pilot who developed symptoms of cardiac infarction while flying over a mountain pass in California. He managed to bring his plane to a landing and died in a hospital a few hours later. At autopsy extensive atheroma of the descending branch of the left coronary artery was found, but there was no myocardial infarction.

Case VII. Coronary Insufficiency Evidenced by Repeated Anginal Attacks at Rest in a Patient with Coronary Artery Sclerosis

The patient was first seen in 1934 at the age of forty-eight years. Four years previously he had had an attack of squeezing substernal pain with difficulty in breathing which lasted a whole day. However, he continued at his work the following day, but ever since experienced similar attacks every few weeks. These attacks came both at rest and on activity. In 1934 the physical examination was completely negative. The heart was not enlarged. The heart sounds were of good quality. The blood pressure in mm. of mercury was 120 systolic and 80 diastolic. The electrocardiogram was normal. Following this visit he was well for two years and in 1936 he experienced a severe attack of substernal pain radiating to the neck and to the palate and associated with a choking sensation. The pain lasted one and a half hours and recurred the same night. Following this he stayed in bed. Examination ten days later again revealed no physical or electrocardiographic abnormalities.

Case V. Coronary Insufficiency Due to Hyperthyroidism Complicating Coronary Artery Sclerosis

A woman, aged sixty-two years, had had a partial thyroidectomy for hyperthyroidism at thirty-four. At the age of fifty-seven she began to complain of exhaustion and mild retrosternal distress on walking eight blocks or so. Examination at that time revealed no evidences of hyperthyroidism. There was some enlargement of the left ventricle. The heart sounds were of good quality. Blood pressure in mm. of mercury was 165 systolic and 90 diastolic. The electrocardiogram was normal. Her symptoms gradually became aggravated and at the age of fifty-nine she was unable to walk more than a block because of sharp substernal pain and inability to breathe. At this time the heart had become larger. The blood pressure was unaltered, but the electrocardiogram revealed bundle branch block. Three months later she felt better and the electrocardiogram had returned to normal. The basal metabolic rate was + 11 per cent.

At the age of sixty, the patient began to be quite nervous, complained of palpitation and tremor of the hands. The pulse rate was 108. There was moderate firm enlargement of the thyroid gland and the basal metabolic rate was + 24 per cent. She was given small doses of Lugol's solution and gained some weight, but palpitation, tachycardia and nervousness persisted and the anginal symptoms remained very incapacitating. After a few months the bundle branch block recurred. In spite of careful medical treatment and prolonged bed rest the cardiac symptoms remained unchanged. Finally a subtotal thyroidectomy was performed. A large nodular goiter was removed. Following this her pulse slowed to 90 and although bundle branch block persisted her cardiac reserve improved greatly and she was able to be up and about and active without anginal symptoms.

Case VI. Coronary Insufficiency with Cardiac Infarction Induced by Severe Hemorrhage

A man, aged fifty-five years, had had symptoms typical of angina pectoris for one year. General physical examination was negative. The left ventricle and left auricle were enlarged. The heart sounds were of good quality. The blood pressure in mm. of mercury was 100 systolic and 60 diastolic. The electrocardiogram showed low T waves in the limb leads, and a deep Q wave in lead IV. His cardiac status remained unchanged for about a year, when he had a severe intestinal hemorrhage with collapse.

ginal attacks at rest without apparent cause and when he is awakened from sleep by such attacks one can be certain that there is far advanced coronary artery disease; that the lumen of at least one of the coronary arteries is so narrowed that it is but a matter of time before a thrombosis will occur within it.

In this case a period of five months elapsed before this actually took place. Usually the period is a shorter one.

Treatment of these patients is difficult and unsatisfactory. It is impossible to restore the lumen of the diseased coronary arteries. One must endeavor to minimize the calls made on the heart and on the coronary flow in the hope that in time a sufficient collateral circulation will develop so that the patient will survive the coronary thrombosis that will inevitably occur. The patient should be kept in bed and should be given a 1200-calorie diet. Abdominal distention must be combated. At times the administration of $\frac{1}{150}$ grain of atropine and $\frac{1}{3}$ grain of phenobarbital three times a day before meals will control gastro-intestinal function and prevent reflex coronary spasm. The patient should be instructed to take nitroglycerin on the slightest indication of anginal distress. Many patients are afraid to take more than one or two tablets of nitroglycerin a day. They should be told that they can take an indefinite number of tablets, that they can only do good and never harm. At times sodium nitrite or erythroltetranitrate given in doses of $\frac{1}{2}$ to 1 grain three or four times a day prevents recurrent attacks. Aminophylline given as the 3-grain enteric-coated tablet or theobromine sodium acetate $7\frac{1}{2}$ grains may be tried but they are usually ineffectual. Often recourse must be had to codeine or morphine when the attacks are severe. With rare exceptions the spontaneous attacks persist until the offending artery has been occluded by a thrombus. If the patient recovers he may be free of attacks.

Case VIII. Coronary Insufficiency in a Patient with Aortic Stenosis

A man who had had rheumatic fever and rheumatic heart disease since childhood had had few symptoms referable to his heart up to his thirty-eighth year. His heart was greatly en-

After a few months' rest the patient returned to work as a typesetter and did fairly well with occasional attacks of substernal pain, not directly related to exertion. In 1938 he began to experience frequent cramping precordial pain with difficulty in breathing coming at rest, or while he was asleep. He also was unable to walk more than three blocks without being stopped by anginal pain. On this occasion, too, the physical examination and the electrocardiogram were normal. In spite of several weeks' bed rest the spontaneous anginal attacks persisted for about three months. In October, 1939, the anginal attacks recurred three or four times a day and often awakened him from sleep.

In spite of bed rest and all types of medication including aminophylline, theobromine, sedatives of all sorts, sodium nitrite and erythroltetranitrate the attacks persisted and indeed became more frequent. In January, 1940, the patient was having fifteen attacks a day. He had returned to work because he found that the attacks came on whether he rested at home or whether he busied himself at his occupation. The physical and electrocardiographic findings were still normal. He was taking about 15 tablets of nitroglycerin daily and was unable to walk more than one-half block without stopping. Finally in April, 1940, he died very suddenly in an attack.

Symptoms of coronary disease in this patient were first noted in 1930 with a prolonged attack of precordial pain. This undoubtedly represented an initial coronary thrombosis. Following this he had symptoms of angina pectoris although there were intervals of several years during which he had no symptoms. In 1936 he apparently experienced another coronary thrombosis. Following this he had more frequent anginal attacks both at rest and on exertion. Finally in October, 1939, he began having very frequent anginal attacks at rest as well as angina on very slight exertion. The spontaneous anginal attacks persisted with great frequency for five months until his death. During this period his coronary flow was so insufficient that the slightest physiological changes in the cirulation limited the blood flow in the coronary arteries to produce anoxemia and pain. He was in a state of chronic coronary insufficiency.

These cases are important to recognize because of their serious prognosis. When a patient experiences frequent an-

ginal attacks at rest without apparent cause and when he is awakened from sleep by such attacks one can be certain that there is far advanced coronary artery disease; that the lumen of at least one of the coronary arteries is so narrowed that it is but a matter of time before a thrombosis will occur within it.

In this case a period of five months elapsed before this actually took place. Usually the period is a shorter one.

Treatment of these patients is difficult and unsatisfactory. It is impossible to restore the lumen of the diseased coronary arteries. One must endeavor to minimize the calls made on the heart and on the coronary flow in the hope that in time a sufficient collateral circulation will develop so that the patient will survive the coronary thrombosis that will inevitably occur. The patient should be kept in bed and should be given a 1200-calorie diet. Abdominal distention must be combated. At times the administration of $\frac{1}{150}$ grain of atropine and $\frac{1}{3}$ grain of phenobarbital three times a day before meals will control gastro-intestinal function and prevent reflex coronary spasm. The patient should be instructed to take nitroglycerin on the slightest indication of anginal distress. Many patients are afraid to take more than one or two tablets of nitroglycerin a day. They should be told that they can take an indefinite number of tablets, that they can only do good and never harm. At times sodium nitrite or erythroltetranitrate given in doses of $\frac{1}{2}$ to 1 grain three or four times a day prevents recurrent attacks. Aminophylline given as the 3-grain enteric-coated tablet or theobromine sodium acetate $7\frac{1}{2}$ grains may be tried but they are usually ineffectual. Often recourse must be had to codeine or morphine when the attacks are severe. With rare exceptions the spontaneous attacks persist until the offending artery has been occluded by a thrombus. If the patient recovers he may be free of attacks.

Case VIII. Coronary Insufficiency in a Patient with Aortic Stenosis

A man who had had rheumatic fever and rheumatic heart disease since childhood had had few symptoms referable to his heart up to his thirty-eighth year. His heart was greatly en-

After a few months' rest the patient returned to work as a typesetter and did fairly well with occasional attacks of substernal pain, not directly related to exertion. In 1938 he began to experience frequent cramping precordial pain with difficulty in breathing coming at rest, or while he was asleep. He also was unable to walk more than three blocks without being stopped by anginal pain. On this occasion, too, the physical examination and the electrocardiogram were normal. In spite of several weeks' bed rest the spontaneous anginal attacks persisted for about three months. In October, 1939, the anginal attacks recurred three or four times a day and often awakened him from sleep.

In spite of bed rest and all types of medication including aminophylline, theobromine, sedatives of all sorts, sodium nitrite and erythroltetranitrate the attacks persisted and indeed became more frequent. In January, 1940, the patient was having fifteen attacks a day. He had returned to work because he found that the attacks came on whether he rested at home or whether he busied himself at his occupation. The physical and electrocardiographic findings were still normal. He was taking about 15 tablets of nitroglycerin daily and was unable to walk more than one-half block without stopping. Finally in April, 1940, he died very suddenly in an attack.

Symptoms of coronary disease in this patient were first noted in 1930 with a prolonged attack of precordial pain. This undoubtedly represented an initial coronary thrombosis. Following this he had symptoms of angina pectoris although there were intervals of several years during which he had no symptoms. In 1936 he apparently experienced another coronary thrombosis. Following this he had more frequent anginal attacks both at rest and on exertion. Finally in October, 1939, he began having very frequent anginal attacks at rest as well as angina on very slight exertion. The spontaneous anginal attacks persisted with great frequency for five months until his death. During this period his coronary flow was so insufficient that the slightest physiological changes in the circulation limited the blood flow in the coronary arteries to produce anoxemia and pain. He was in a state of chronic coronary insufficiency.

These cases are important to recognize because of their serious prognosis. When a patient experiences frequent an-

ginal attacks at rest without apparent cause and when he is awakened from sleep by such attacks one can be certain that there is far advanced coronary artery disease; that the lumen of at least one of the coronary arteries is so narrowed that it is but a matter of time before a thrombosis will occur within it.

In this case a period of five months elapsed before this actually took place. Usually the period is a shorter one.

Treatment of these patients is difficult and unsatisfactory. It is impossible to restore the lumen of the diseased coronary arteries. One must endeavor to minimize the calls made on the heart and on the coronary flow in the hope that in time a sufficient collateral circulation will develop so that the patient will survive the coronary thrombosis that will inevitably occur. The patient should be kept in bed and should be given a 1200-calorie diet. Abdominal distention must be combated. At times the administration of $\frac{1}{150}$ grain of atropine and $\frac{1}{3}$ grain of phenobarbital three times a day before meals will control gastro-intestinal function and prevent reflex coronary spasm. The patient should be instructed to take nitroglycerin on the slightest indication of anginal distress. Many patients are afraid to take more than one or two tablets of nitroglycerin a day. They should be told that they can take an indefinite number of tablets, that they can only do good and never harm. At times sodium nitrite or erythroltetranitrate given in doses of $\frac{1}{2}$ to 1 grain three or four times a day prevents recurrent attacks. Aminophylline given as the 3-grain enteric-coated tablet or theobromine sodium acetate $7\frac{1}{2}$ grains may be tried but they are usually ineffectual. Often recourse must be had to codeine or morphine when the attacks are severe. With rare exceptions the spontaneous attacks persist until the offending artery has been occluded by a thrombus. If the patient recovers he may be free of attacks.

Case VIII. Coronary Insufficiency in a Patient with Aortic Stenosis

A man who had had rheumatic fever and rheumatic heart disease since childhood had had few symptoms referable to his heart up to his thirty-eighth year. His heart was greatly en-

larged, particularly the left ventricle. At the aortic area a rough systolic thrill was palpable and a harsh systolic murmur was audible. There was also a diastolic murmur which was transmitted down the sternum. One day he developed complete heart block with a heart rate of 40. With this he complained of typical angina pectoris on slight exertion. The heart block disappeared and his anginal symptoms were relieved. This sequence recurred several times. Subsequently he developed lobar pneumonia and at the height of his febrile reaction he suddenly developed intense epigastric and substernal pain followed by shock and death within an hour. At autopsy the coronary arteries were found to be normal. There was a tight calcific aortic stenosis.

Coronary insufficiency occurs commonly in patients with aortic stenosis. Aortic stenosis interferes with the coronary circulation in the same way as does coronary sclerosis. When the aortic orifice is narrowed the blood supply to both coronary arteries is impaired, and when the heart is compelled to do more work the stenosed orifice does not admit an adequate amount of blood, so that insufficiency of the whole coronary circulation results. It is understandable, therefore, why so many patients with aortic stenosis have symptoms of angina pectoris and why sudden death is such a common termination of these cases.

The last case illustrates two mechanisms that may give rise to coronary insufficiency. First, the sudden halving of the heart rate prevented the adequate flow of blood through the coronary arteries and this resulted in anginal pain on minimal effort. Secondly, the great demands made on the heart as a result of a severe lobar pneumonia caused severe coronary insufficiency of sufficient intensity to cause death.

TREATMENT OF CORONARY INSUFFICIENCY

These syndromes of coronary insufficiency are of the greatest clinical importance. They indicate a precarious state of the coronary circulation, and reveal the factors that may cause serious cardiac damage by overtaxing the impaired coronary arterial bed. Prolonged coronary insufficiency may, as has been shown, cause cardiac infarction even in the absence of coronary occlusion.

Regulation of the Patient's Life.—Recognition of the mechanisms of coronary insufficiency, therefore, enables the physician to regulate his patient's life with a view to preventing further cardiac damage or death.

Overexertion and emotional stress are the commonest causes of coronary insufficiency, and must be completely eliminated from the life of the patient with coronary artery disease, or with aortic stenosis. That does not mean that the patient should be condemned to a life of invalidism and complete retirement from work. Most persons with coronary disease can carry on prolonged, measured leisurely activity without harm to themselves. They must avoid spurts of effort such as running, or lifting, they must not overeat and overdrink, they must try to escape emotional crises. When anginal pain is induced by minor activities, or when it comes while the patient is at rest, it indicates advanced narrowing of the coronary arteries. In such cases complete rest and immobilization is called for, in the hope that with time a collateral arterial bed will develop to compensate for the stenosed coronary arteries.

Patients with Abnormal Heart Rhythms.—Often it is possible to prevent and control abnormal heart rhythms that decrease the coronary blood flow by inducing a rapid ineffectual beating of the heart. The occurrence of extrasystoles may give warning of the possible occurrence of paroxysmal tachycardia or auricular fibrillation. The administration of 3 grains of *quinidine sulfate* three or four times a day often abolishes extrasystoles and prevents the occurrence of paroxysmal rapid rhythms.

Patients Who Require Operation.—With the knowledge that shock and hemorrhage may induce coronary insufficiency the doctor will try to spare his patients with coronary disease all but essential operations. Operations of election, such as herniotomies, should not be performed. When operation becomes necessary it is essential to have an excellent anesthetist and a skilled surgeon and minimum trauma and bleeding.

Constitutional disorders such as anemia or hyperthyroidism overtax the heart and may lead to coronary insufficiency

larged, particularly the left ventricle. At the aortic area a rough systolic thrill was palpable and a harsh systolic murmur was audible. There was also a diastolic murmur which was transmitted down the sternum. One day he developed complete heart block with a heart rate of 40. With this he complained of typical angina pectoris on slight exertion. The heart block disappeared and his anginal symptoms were relieved. This sequence recurred several times. Subsequently he developed lobar pneumonia and at the height of his febrile reaction he suddenly developed intense epigastric and substernal pain followed by shock and death within an hour. At autopsy the coronary arteries were found to be normal. There was a tight calcific aortic stenosis.

Coronary insufficiency occurs commonly in patients with aortic stenosis. Aortic stenosis interferes with the coronary circulation in the same way as does coronary sclerosis. When the aortic orifice is narrowed the blood supply to both coronary arteries is impaired, and when the heart is compelled to do more work the stenosed orifice does not admit an adequate amount of blood, so that insufficiency of the whole coronary circulation results. It is understandable, therefore, why so many patients with aortic stenosis have symptoms of angina pectoris and why sudden death is such a common termination of these cases.

The last case illustrates two mechanisms that may give rise to coronary insufficiency. First, the sudden halving of the heart rate prevented the adequate flow of blood through the coronary arteries and this resulted in anginal pain on minimal effort. Secondly, the great demands made on the heart as a result of a severe lobar pneumonia caused severe coronary insufficiency of sufficient intensity to cause death.

TREATMENT OF CORONARY INSUFFICIENCY

These syndromes of coronary insufficiency are of the greatest clinical importance. They indicate a precarious state of the coronary circulation, and reveal the factors that may cause serious cardiac damage by overtaxing the impaired coronary arterial bed. Prolonged coronary insufficiency may, as has been shown, cause cardiac infarction even in the absence of coronary occlusion.

Regulation of the Patient's Life.—Recognition of the mechanisms of coronary insufficiency, therefore, enables the physician to regulate his patient's life with a view to preventing further cardiac damage or death.

Overexertion and emotional stress are the commonest causes of coronary insufficiency, and must be completely eliminated from the life of the patient with coronary artery disease, or with aortic stenosis. That does not mean that the patient should be condemned to a life of invalidism and complete retirement from work. Most persons with coronary disease can carry on prolonged, measured leisurely activity without harm to themselves. They must avoid spurts of effort such as running, or lifting, they must not overeat and overdrink, they must try to escape emotional crises. When anginal pain is induced by minor activities, or when it comes while the patient is at rest, it indicates advanced narrowing of the coronary arteries. In such cases complete rest and immobilization is called for, in the hope that with time a collateral arterial bed will develop to compensate for the stenosed coronary arteries.

Patients with Abnormal Heart Rhythms.—Often it is possible to prevent and control abnormal heart rhythms that decrease the coronary blood flow by inducing a rapid ineffectual beating of the heart. The occurrence of extrasystoles may give warning of the possible occurrence of paroxysmal tachycardia or auricular fibrillation. The administration of 3 grains of *quinidine sulfate* three or four times a day often abolishes extrasystoles and prevents the occurrence of paroxysmal rapid rhythms.

Patients Who Require Operation.—With the knowledge that shock and hemorrhage may induce coronary insufficiency the doctor will try to spare his patients with coronary disease all but essential operations. Operations of election, such as herniotomies, should not be performed. When operation becomes necessary it is essential to have an excellent anesthetist and a skilled surgeon and minimum trauma and bleeding.

Constitutional disorders such as anemia or hyperthyroidism overtax the heart and may lead to coronary insufficiency

larged, particularly the left ventricle. At the aortic area a rough systolic thrill was palpable and a harsh systolic murmur was audible. There was also a diastolic murmur which was transmitted down the sternum. One day he developed complete heart block with a heart rate of 40. With this he complained of typical angina pectoris on slight exertion. The heart block disappeared and his anginal symptoms were relieved. This sequence recurred several times. Subsequently he developed lobar pneumonia and at the height of his febrile reaction he suddenly developed intense epigastric and substernal pain followed by shock and death within an hour. At autopsy the coronary arteries were found to be normal. There was a tight calcific aortic stenosis.

Coronary insufficiency occurs commonly in patients with aortic stenosis. Aortic stenosis interferes with the coronary circulation in the same way as does coronary sclerosis. When the aortic orifice is narrowed the blood supply to both coronary arteries is impaired, and when the heart is compelled to do more work the stenosed orifice does not admit an adequate amount of blood, so that insufficiency of the whole coronary circulation results. It is understandable, therefore, why so many patients with aortic stenosis have symptoms of angina pectoris and why sudden death is such a common termination of these cases.

The last case illustrates two mechanisms that may give rise to coronary insufficiency. First, the sudden halving of the heart rate prevented the adequate flow of blood through the coronary arteries and this resulted in anginal pain on minimal effort. Secondly, the great demands made on the heart as a result of a severe lobar pneumonia caused severe coronary insufficiency of sufficient intensity to cause death.

TREATMENT OF CORONARY INSUFFICIENCY

These syndromes of coronary insufficiency are of the greatest clinical importance. They indicate a precarious state of the coronary circulation, and reveal the factors that may cause serious cardiac damage by overtaxing the impaired coronary arterial bed. Prolonged coronary insufficiency may, as has been shown, cause cardiac infarction even in the absence of coronary occlusion.

CARDIAC ANEURYSM*

DAVID SCHERF, M.D.†

and

LINN J. BOYD, M.D., F.A.C.P.‡

CARDIAC aneurysm perfectly exemplifies the fact that even experienced physicians regard a condition as rare if they do not learn to look especially for it. Aneurysmal dilatation of a circumscribed portion of the ventricular wall was described more than 185 years ago by Galeati and Hunter. Despite many subsequent post-mortem observations, the first confirmed ante-mortem diagnosis was not made until 1896 when Remlinger was successful. In 1926 Pletnew compiled the reported cases and found that the correct clinical diagnosis had been reached only six times in 300 examples of the lesion. Shortly thereafter clinical reports of recognized cases rapidly multiplied and at present every cardiologist usually has several cases under observation. Roentgenology is responsible for a definite percentage of these ante-mortem diagnoses.

ILLUSTRATIVE CASES

CASE I.—C. R. was a fifty-eight-year-old male who had suffered six years ago from a severe attack of angina pectoris lasting for twenty-four hours. When seen eight days after that attack he presented all of the customary signs of coronary thrombosis; the blood pressure had fallen to 80 mm. of mercury systolic and 70 diastolic and the heart sounds were practically inaudible. At this time a circumscribed pulsation could be felt somewhat above and mesial to the apex. Six weeks later at a second ex-

*From the Department of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals (Metropolitan Hospital Service).

† Associate Clinical Professor of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals; Visiting Physician and Chief of Section on Cardiology, Metropolitan Hospital.

‡ Professor of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals; Director of Medicine, Metropolitan Hospital.

in the presence of coronary artery sclerosis. Such conditions must be corrected and under these circumstances operation may become necessary. Subtotal thyroidectomy must be done in the presence of hyperthyroidism and bleeding fibroids or hemorrhoids must be removed if they do not yield to conservative treatment.

High Flights Are Contraindicated.—Patients with coronary disease should not take airplane flights at altitudes above 10,000 feet.

Patients with Coronary Artery Disease.—The nitrites are very valuable in tiding patients with coronary artery disease over periods of coronary insufficiency. They may be given freely for the relief and prevention of pain. *Nitroglycerin* in doses of $\frac{1}{150}$ to $\frac{1}{100}$ grain should be administered whenever there is pain. When spontaneous anginal pain recurs several times a day, *sodium nitrite* or *erythroltetranitrate* in $\frac{1}{2}$-grain doses three or four times a day is very useful.

BIBLIOGRAPHY

1. Blumgart, H. L., Schlesinger, M. J. and Zoll, P. M.: Multiple Fresh Coronary Occlusions in Patients with Antecedent Shock. Arch. Int. Med., *68:* 181, 1941.
2. Benson, O. V. J.: Coronary Artery Disease. Report of Fatal Attack in a Pilot While Flying. J. Aviation Med., *8:* 81, 1937.

Lead I was displaced slightly above the base line and there was no T wave. In Leads II and III the S-T segment was slightly depressed and the T wave was low but positive. The chest lead (CR_2) showed an abnormally low R wave. Tracings obtained six years later, two months before death (Fig. 148), were identical with the early records.

Re-examination at regular short intervals revealed no change in the clinical, x-ray, or electrocardiographic status. The blood pressure varied between 100/80 and 130/90. The pulsation never receded but the diastolic murmur became inaudible from time to time.

The patient remained free from symptoms until August, 1941. At that time he experienced pain in the right flank which was recognized as a retrocecal appendicitis after some delay. The day before the scheduled operation, a series of short attacks of paroxysmal tachycardia developed. Administration of quinidine failed to control the arrhythmia and the patient died suddenly, six years after the appearance of the aneurysm.

CASE II.—This forty-five-year-old patient also had his attack six years ago, approximately one month before the patient of Case I. He also had had a severe attack of coronary thrombosis which lowered the systolic blood pressure level to 80 mm. Hg. The severity of the attack, the rapidly appearing cardiac dilatation and the development of a systolic pulsation above the cardiac apex four weeks after the coronary thrombosis, despite strict bed rest, necessitated maintenance of bed rest for a long time. Six months elapsed before the heart sounds became loud and the blood pressure rose to 100–105 mm. of mercury systolic and 80 diastolic.

The abnormal pulsation disappeared about four months after it was first seen but the heart remained permanently widened to the left. A systolic murmur was audible at the apex and at the pulsating area but no diastolic murmur was ever heard. No projection of the heart wall was perceptible but a definite absence of pulsations at the left lower cardiac border was demonstrable on fluoroscopy.

Two months after the attack the first electrocardiogram was obtained. A slow regular sinus rhythm with a normal conduction time of 0.17 second was found. There was an unusually deep Q wave in Lead I and deep S waves in Leads II and III. The initial complex was neither widened nor split but the T wave in Lead I was inverted.

amination this pulsation had increased so that the diameter of this impulse was 4½ cm. Mere inspection revealed a hemispherical bulging in this region during systole. A systolic and a soft diastolic murmur was audible over the pulsation.

The low blood pressure, the very soft heart sounds and the early appearance of a cardiac aneurysm were adequate reasons for insisting upon a prolonged period of bed rest which amounted to four months. X-ray facilities were not available so that this
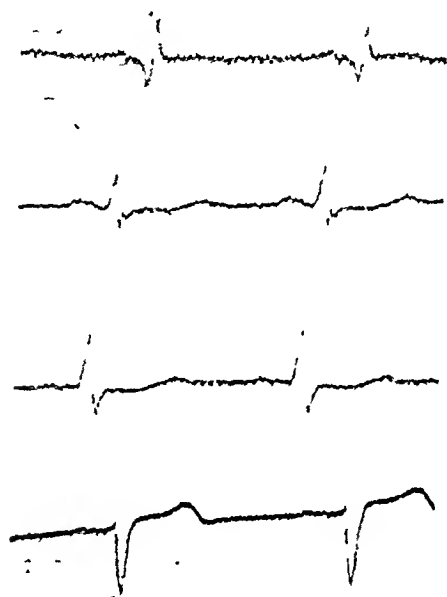
Fig. 148.—Electrocardiogram in partial cardiac aneurysm.

examination was postponed until the patient was allowed out of bed. This revealed an enlargement of the left ventricle and a bulge at the left lower segment of the cardiac contour; the pulsation was palpable somewhat mesial and above the site of the pouch.

The electrocardiogram showed a regular sinus rhythm with normal conduction time. The initial complex had a deep Q wave in Lead I and was 0.10 second wide. The S-T segment in

Lead I was displaced slightly above the base line and there was no T wave. In Leads II and III the S-T segment was slightly depressed and the T wave was low but positive. The chest lead (CR$_2$) showed an abnormally low R wave. Tracings obtained six years later, two months before death (Fig. 148). were identical with the early records.

Re-examination at regular short intervals revealed no change in the clinical, x-ray, or electrocardiographic status. The blood pressure varied between 100/80 and 130/90. The pulsation never receded but the diastolic murmur became inaudible from time to time.

The patient remained free from symptoms until August, 1941. At that time he experienced pain in the right flank which was recognized as a retrocecal appendicitis after some delay. The day before the scheduled operation. a series of short attacks of paroxysmal tachycardia developed. Administration of quinidine failed to control the arrhythmia and the patient died suddenly, six years after the appearance of the aneurysm.

Case II.—This forty-five-year-old patient also had his attack six years ago. approximately one month before the patient of Case I. He also had had a severe attack of coronary thrombosis which lowered the systolic blood pressure level to 80 mm. Hg. The severity of the attack. the rapidly appearing cardiac dilatation and the development of a systolic pulsation above the cardiac apex four weeks after the coronary thrombosis. despite strict bed rest. necessitated maintenance of bed rest for a long time. Six months elapsed before the heart sounds became loud and the blood pressure rose to 100–105 mm. of mercury systolic and 80 diastolic.

The abnormal pulsation disappeared about four months after it was first seen but the heart remained permanently widened to the left. A systolic murmur was audible at the apex and at the pulsating area but no diastolic murmur was ever heard. No projection of the heart wall was perceptible but a definite absence of pulsations at the left lower cardiac border was demonstrable on fluoroscopy.

Two months after the attack the first electrocardiogram was obtained. A slow regular sinus rhythm with a normal conduction time of 0.17 second was found. There was an unusually deep Q wave in Lead I and deep S waves in Leads II and III. The initial complex was neither widened nor split but the T wave in Lead I was inverted.

The patient has been persistently free from symptoms and is active. At present, six years after the acute occlusion, the elec-

Fig. 149.—(See text.)

trocardiogram remains the same as two months after the episode occurred (Fig. 149).

INCIDENCE; PATHOLOGY

In a vast majority of the cases cardiac aneurysm results from *coronary occlusion* and *myomalacia*. Severe rheumatic myocarditis, gumma and mycotic inflammations of the myocardium are mentioned as occasional etiologic factors but in the following remarks the discussion will be limited to aneurysms consequent to myomalacia (myocardial infarction). Opinions regarding the incidence of cardiac aneurysm vary. According to Parkinson, Beford and Thompson it occurs in 9 per cent of patients with coronary occlusion but Klemperer states that 38 per cent is more nearly correct. In our experience the latter estimate closely approximates the true incidence. Accordingly, one must consider this development in practically every third individual who suffers from an occlusion of a large branch of a coronary artery. Only a small percentage of these cases can be recognized ante mortem.

Clinical as well as experimental observations indicate that a cardiac aneurysm is more prone to occur when the patient fails to remain in bed for a sufficiently long time after coronary occlusion and when the heart must work against great resistance (hypertension). However, we have seen cardiac aneurysms develop despite strict maintenance of bed rest and when low blood pressure values prevailed.

Cardiac aneurysms are found almost exclusively in the *left* ventricle. They are most commonly associated with infarction near but above the apex, on the anterior wall. Although posterior wall infarction is almost as common as anterior wall infarction, it is more rarely followed by aneurysm.

The bulge caused by the aneurysm at times is so slight that the cardiac contour is scarcely altered since the wall of the aneurysm is only slightly thinner than the remainder of the ventricle. Under such circumstances the true situation is discovered only when the pathologist opens the heart. In other cases, however, there is a massive *aneurysmal sac*. It is not unusual for it to measure 5 cm. in diameter and in one instance this measurement reached 16 cm. Sometimes the sac is filled by a *thrombus* and this may be responsible for emboli in the systemic circulation. The thrombus may become calcified and the ventricular wall may be represented only by a mass of connective tissue in some areas. Usually, but not invariably, *pericardial adhesions* exist at the site of the aneurysm. If present, this adhesive pericarditis represents a very useful complication since it supports the wall of the aneurysm. In a patient observed by us, the myocardium was perforated at one point but the site of perforation was covered solely by thin pericardium. As a rule *the heart is enlarged.*

Since coronary thrombosis is more common in males, aneurysms of the heart are more frequently observed in this sex.

SYMPTOMS AND SIGNS

Ordinarily the history reveals indications of an acute coronary occlusion. Nevertheless, it is noteworthy that sometimes pain is not mentioned. It is precisely in these cases that no rest was prescribed just at the time it was most needed

so that an aneurysm is often the result. The aneurysm itself causes no symptoms. Some patients feel remarkably good and cannot understand why the physician insists upon any restrictions. Sooner or later many develop signs of left ventricular failure. *Extrasystoles* or attacks of *paroxysmal tachycardia* are common. Usually it concerns ventricular extrasystoles and ventricular tachycardias. In rare cases the patient becomes aware of the abnormal pulsation on the chest wall and is disturbed by it. Therefore, no symptoms can be called typical of a cardiac aneurysm.

Since the efforts of Aran in 1864 frequently an attempt has been made to elaborate upon the *physical signs* of cardiac aneurysm. Most often the disproportion between the augmented apical impulse and the weak radial pulse is stressed. With some limitations and supplementations this is correct. Nevertheless one should not forget that a markedly increased apical impulse and a small pulse are found in an advanced and silent aortic stenosis. On the other hand, in some cases of coronary thrombosis the pulse pressure is not small and consequently the pulse is not weak when aneurysm is present.

Despite these exceptions, the rule is valid, namely, when no cause can be found for a marked systolic and abnormally located *pulsation of the heart*, one should suspect the possibility of a cardiac aneurysm. These pulsations may be remarkably strong, difficult to suppress, heaving and slow as in a massive cardiac hypertrophy. Personal observations indicate it may develop as early as five days after coronary thrombosis in some patients while in others several weeks may elapse. It is not felt "over the precordium" nor "between the apex and the sternum" as often stated; rather its location is very characteristic. Usually the pulsation is noted *above* the apex along the left cardiac border, the apex having been accurately located by palpation, percussion or fluoroscopy. Accordingly, it is too high for an apical impulse and too low for a pulsation of the Conus pulmonalis. Moreover it is not found over the "precordium" where the pulsation of right heart hypertrophy or the pulsations in the excitable heart (hyperthyroidism, beri-beri, neurocirculatory asthe-

nia) are perceived. In some patients the pulsation is barely palpable but in others it is very distinct; it gives the impression of a bulging hemisphere. Ordinarily the pulsation increases in intensity soon after its first appearance and persists until death without change; it may diminish or even disappear. This happens, as two personal observations indicate, when gradual scarring occurs and is followed by contraction of connective tissue. Likewise the formation of a thrombus in the aneurysmal sac may explain the disappearance of the pulsation.

Pulsations may be entirely absent when a lateral or posterior aneurysm develops; these cases are not rare.

Percussion suggests cardiac enlargement but is otherwise not informative.

Auscultation may be very important in the diagnosis. As a rule one hears a *systolic murmur* which, by itself, is not characteristic. It is, however, particularly loud over the pulsation and sounds close to the ear. Moreover a *diastolic murmur* is audible over the pulsation; it is very high pitched and closely resembles the diastolic murmur of aortic insufficiency. In two patients observed by us a diagnosis of a rheumatic mitral-aortic lesion was assumed on the basis of a left parasternal diastolic murmur and a systolic apical murmur; necropsy revealed a partial cardiac aneurysm following coronary thrombosis. The diastolic murmur is heard only when the aneurysm pulsates strongly, that is, only in patients with a large aneurysm of the anterior wall of the left ventricle; however, it is not invariable even when these requirements are met. Nevertheless it is an important and relatively common diagnostic sign. It is of interest that when the first confirmed antemortem diagnosis of a cardiac aneurysm was made in 1896 by Remlinger, a French military surgeon, this murmur was heard. Although its presence was often confirmed in the following years, recent papers on this subject fail to mention it. The origin of this murmur is not entirely clear.

X-RAY EXAMINATION; ELECTROCARDIOGRAPHY

X-ray examination may be of assistance in many cases. However, it should be immediately emphasized that positive

findings are rarely obtained by a simple posterior-anterior plate. An irregularity of the left border of the heart or a circumscribed bulge may facilitate the diagnosis or establish it by a mere glance. However, slight irregularities of the left ventricular border may have another genesis, for example, pleuropericardial adhesions may be responsible. Often the cardiac apex is invisible, since it is concealed in the diaphragmatic-abdominal shadows. In these cases Parkinson and his associates recommend *fluoroscopy* after inflation of the stomach by means of sodium bicarbonate. A sharply pointed left lower cardiac contour with local absence of pulsation may be produced by a collection of fat at the apex as described by G. Schwartz. Under these circumstances it will be noted upon closer examination that the triangular shadow has diminished density and the normal cardiac apex can be detected through the fat shadow. Circumscribed bulging which develops in the posterior or anterior planes is demonstrable by examination in the oblique positions.

Not rarely the bulging area merges so imperceptibly with the adjoining healthy ventricular wall that one finds only an enlarged heart. In some of these cases systolic outpouching in place of systolic reduction has been described and absence of pulsations has been emphasized by Schilling (1933). These signs are stressed especially by those observers who have studied the movements of the cardiac border by means of the kymogram.

In the interpretation and evaluation of the absence of cardiac pulsations at the left lower cardiac border, one must bear in mind that *visible* pulsations may be *normally* absent in this area. The heart contracts in a longitudinal as well as transverse direction during systole and rotates around its axis so that entirely different sections of the left ventricle form the left border of the heart at different moments. The interference created by all these movements may result in a pseudo-standstill of the left cardiac border. On the other hand, it is possible for pulsations to be transmitted when there is necrosis of a part of the left ventricular wall.

Not rarely *calcium deposits* are observed in the region of an aneurysm. As a rule they arise from calcified *thrombi*.

They must be distinguished from the calcifications of the pericardium in adhesive pericarditis and from calcified valves after rheumatic fever.

The *electrocardiogram* may show the signs of an anterior wall infarction or, more rarely, of a posterior wall lesion. Like an uncomplicated coronary thrombosis, infarctions followed by aneurysms are accompanied by wide variety of electrocardiographic changes. Thus, two of our cases presented a block of the right bundle branch. There is, however, no electrocardiogram typical of cardiac aneurysm. Nevertheless it is remarkable how often one picture, otherwise uncommon, is encountered: there is a very deep Q wave in Lead I and the S-T segment is slightly elevated (Fig. 148), so that one is inclined to assume a recent infarction. However, the electrocardiogram retains the same appearance for years.

PROGNOSIS AND TREATMENT

The *prognosis* is dubious in all cases of cardiac aneurysm. Although it is not rare for patients to lead a normal and active life, free from symptoms for years, this is exceptional. In three personally observed cases and in several instances mentioned in the literature, paroxysmal ventricular tachycardias developed near the end and probably death was caused by ventricular fibrillation. It is recommended that ventricular extrasystoles and tachycardias in these cases be immediately and energetically treated with quinidine.

There is no special *treatment* which is specific for cardiac aneurysms. Extreme care in regard to physical effort is necessary. However, the cases reported in this discussion show that patients with cardiac aneurysms may feel well and may be active for years providing they avoid severe exertion.

findings are rarely obtained by a simple posterior-anterior plate. An irregularity of the left border of the heart or a circumscribed bulge may facilitate the diagnosis or establish it by a mere glance. However, slight irregularities of the left ventricular border may have another genesis, for example, pleuropericardial adhesions may be responsible. Often the cardiac apex is invisible, since it is concealed in the diaphragmatic-abdominal shadows. In these cases Parkinson and his associates recommend *fluoroscopy* after inflation of the stomach by means of sodium bicarbonate. A sharply pointed left lower cardiac contour with local absence of pulsation may be produced by a collection of fat at the apex as described by G. Schwartz. Under these circumstances it will be noted upon closer examination that the triangular shadow has diminished density and the normal cardiac apex can be detected through the fat shadow. Circumscribed bulging which develops in the posterior or anterior planes is demonstrable by examination in the oblique positions.

Not rarely the bulging area merges so imperceptibly with the adjoining healthy ventricular wall that one finds only an enlarged heart. In some of these cases systolic outpouching in place of systolic reduction has been described and absence of pulsations has been emphasized by Schilling (1933). These signs are stressed especially by those observers who have studied the movements of the cardiac border by means of the kymogram.

In the interpretation and evaluation of the absence of cardiac pulsations at the left lower cardiac border, one must bear in mind that *visible* pulsations may be *normally* absent in this area. The heart contracts in a longitudinal as well as transverse direction during systole and rotates around its axis so that entirely different sections of the left ventricle form the left border of the heart at different moments. The interference created by all these movements may result in a pseudo-standstill of the left cardiac border. On the other hand, it is possible for pulsations to be transmitted when there is necrosis of a part of the left ventricular wall.

Not rarely *calcium deposits* are observed in the region of an aneurysm. As a rule they arise from calcified thrombi.

RECENT ADVANCES IN DIGITALIS THERAPY WITH PARTICULAR ATTENTION TO THE USE OF PURE GLYCOSIDES*

ARTHUR C. DeGRAFF, M.D.†

and

ROBERT C. BATTERMAN, M.D.‡

From the point of view of the practicing physician, there are three important epochs in digitalis therapy. The first was the clear description of the medical use of digitalis by William Withering in 1785. The second was the first biological assay by Houghton in 1898. The third is the identification of the individual glycosides and their availability for general clinical use.

It was the custom prior to Withering to give digitalis to the point of violent vomiting and purging. Thus the diuretic effect was overlooked. The accurate clinical observations of Withering[1] for the first time provided data for the proper indications for its use and method of administration. It is not generally appreciated, however, that he could not have done so unless he were assured of preparations of digitalis of constant potency. Since Withering was a botanist as well as a physician, he was able to obtain a uniformly potent leaf by using only such samples of digitalis as were grown under constant conditions of soil, time of planting, drying of leaves, and so forth. One example may be used to illustrate how his botanical knowledge was of help to therapeutics. It had been

* From the Department of Therapeutics, New York University College of Medicine and the Third Medical Division (New York University). Bellevue Hospital.

† Samuel A. Brown Professor of Therapeutics and Chief of the Cardiac Clinic, New York University College of Medicine; Visiting Physician, Bellevue Hospital.

‡ Assistant in Therapeutics, New York University College of Medicine; Clinical Assistant Visiting Physician, Bellevue Hospital.

RECENT ADVANCES IN DIGITALIS THERAPY WITH PARTICULAR ATTENTION TO THE USE OF PURE GLYCOSIDES*

ARTHUR C. DeGRAFF, M.D.†

and

ROBERT C. BATTERMAN, M.D.‡

FROM the point of view of the practicing physician, there are three important epochs in digitalis therapy. The first was the clear description of the medical use of digitalis by William Withering in 1785. The second was the first biological assay by Houghton in 1898. The third is the identification of the individual glycosides and their availability for general clinical use.

It was the custom prior to Withering to give digitalis to the point of violent vomiting and purging. Thus the diuretic effect was overlooked. The accurate clinical observations of Withering[1] for the first time provided data for the proper indications for its use and method of administration. It is not generally appreciated, however, that he could not have done so unless he were assured of preparations of digitalis of constant potency. Since Withering was a botanist as well as a physician, he was able to obtain a uniformly potent leaf by using only such samples of digitalis as were grown under constant conditions of soil, time of planting, drying of leaves, and so forth. One example may be used to illustrate how his botanical knowledge was of help to therapeutics. It had been

* From the Department of Therapeutics, New York University College of Medicine and the Third Medical Division (New York University), Bellevue Hospital.

† Samuel A. Brown Professor of Therapeutics and Chief of the Cardiac Clinic, New York University College of Medicine; Visiting Physician, Bellevue Hospital.

‡ Assistant in Therapeutics, New York University College of Medicine; Clinical Assistant Visiting Physician, Bellevue Hospital.

the custom to use the roots of many plants, foxglove included, for medical purposes. Withering pointed out quite properly that preparations made from roots of diennial plants, such as digitalis, are inconstant in their potency. He thus made the first great advance in the use of digitalis by emphasizing the necessity for uniform methods of growth and collection of leaves.

BIO-ASSAYS OF DIGITALIS

It is interesting to note that no further advance was made in regard to obtaining a uniformly potent preparation of digitalis in spite of the increasing knowledge of the pharmacologic action of the drug until Houghton[2] in 1898, over 100 years later, described a biological method of assay of digitalis and digitalis-like substances in the frog. In his paper in which he described his method, a *frog assay* whose end-point was death of the frog, he states that he obtained three different samples of strophanthin "from the best manufacturing chemists in the world," and although these were supposed to be pure strophanthin, yet one sample was *ninety times as strong as another*. The others varied between these limits. The samples of digitalis also studied varied greatly in strength, but much less than strophanthin. In pointing out the absolute necessity for the bio-assay of digitalis bodies, Houghton concludes his article with the following statement: "Both strophanthin and digitalis are given daily in tablet or pill form, the amount of active ingredient being apportioned by weight —a splendid opportunity for a sudden termination of a favorably progressing heart disease, should the patient be obliged to have his prescription refilled from a fresh bottle."

Such is the inertia of official bodies that no biological standardization of digitalis appeared in the U. S. Pharmacopoeia until 1916. An assay based on the one-hour frog method in which the frog's heart is examined at the end of one hour is still official.

Clinicians for over two decades have found that the *cat assay* of Hatcher and Brody[3] was superior to the frog assay in that it gave information which aided in the clinical use of the drug. Recently Gold and associates[4] proved this in a

few crucial experiments on selected patients, using the same patient for comparison of the potency of different preparations. It was chiefly on this evidence that the Committee on Bio-assay of the U. S. Pharmacopoeia XII has recommended that the cat assay replace the frog method. The unit will not be an absolute one based on the amount to kill one kilogram of cat, but will be a relative one based on a comparative assay run simultaneously on the official U.S.P. powder. The term "digitalis unit" will, therefore, replace the term "cat unit."

NATURE OF THE CARDIAC GLYCOSIDES

Digitalis powdered leaf is a complex mixture of a number of substances. The substances of interest to us from the cardiac point of view are the glycosides. The term "glycoside" is applied to a large group of substances which, upon hydrolysis, will yield a sugar. This is a general name for the group irrespective of the sugar present, and the term "glucoside" is reserved as the specific name for those glycosides, the sugar constituent of which is glucose. Since the essential sugars in the cardiac glycosides are desoxy sugars and not glucose, although glucose may occasionally be present, the correct term is "cardiac glycoside," not "cardiac glucoside."

The cardiac glycosides (Fig. 150) have a sterol nucleus and, therefore, are related to the D vitamins, estrogens, androgens and cortical hormones. In addition, the genin or aglycone portion of the cardiac glycoside contains a butyro-lactone ring. Variations in substituent groups on the steroid nucleus make possible different genins. The genins possess very weak digitalis-like action and are rapidly eliminated from the body. The addition of the desoxy sugars to position 3 on the genin markedly enhances the potency of the genin. Further addition of glucose does not increase the potency, and may even decrease it.[5]

In digitalis powdered leaf there are at least three different cardiac glycosides, each one of which has different chemical, physical and pharmacological properties such as variations in absorption and elimination. To complicate matters further, we might have different degrees of hydrolysis of each glyco-

the custom to use the roots of many plants, foxglove included, for medical purposes. Withering pointed out quite properly that preparations made from roots of diennial plants, such as digitalis, are inconstant in their potency. He thus made the first great advance in the use of digitalis by emphasizing the necessity for uniform methods of growth and collection of leaves.

BIO-ASSAYS OF DIGITALIS

It is interesting to note that no further advance was made in regard to obtaining a uniformly potent preparation of digitalis in spite of the increasing knowledge of the pharmacologic action of the drug until Houghton[2] in 1898, over 100 years later, described a biological method of assay of digitalis and digitalis-like substances in the frog. In his paper in which he described his method, a *frog assay* whose end-point was death of the frog, he states that he obtained three different samples of strophanthin "from the best manufacturing chemists in the world," and although these were supposed to be pure strophanthin, yet one sample was *ninety times as strong as another*. The others varied between these limits. The samples of digitalis also studied varied greatly in strength, but much less than strophanthin. In pointing out the absolute necessity for the bio-assay of digitalis bodies, Houghton concludes his article with the following statement: "Both strophanthin and digitalis are given daily in tablet or pill form, the amount of active ingredient being apportioned by weight —a splendid opportunity for a sudden termination of a favorably progressing heart disease, should the patient be obliged to have his prescription refilled from a fresh bottle."

Such is the inertia of official bodies that no biological standardization of digitalis appeared in the U. S. Pharmacopoeia until 1916. An assay based on the one-hour frog method in which the frog's heart is examined at the end of one hour is still official.

Clinicians for over two decades have found that the *cat assay* of Hatcher and Brody[3] was superior to the frog assay in that it gave information which aided in the clinical use of the drug. Recently Gold and associates[4] proved this in a

TABLE 1

CHEMICAL RELATIONSHIPS OF THE GLYCOSIDES OF DIGITALIS PURPUREA

Purpurea glycoside A $\xrightarrow{-\text{glucose}}$ Digitoxin $\xrightarrow{-3 \text{ digitoxose}}$ Digitoxigenin

Purpurea glycoside B $\xrightarrow{-\text{glucose}}$ Gitoxin $\xrightarrow{-3 \text{ digitoxose}}$ Gitoxigenin

Glycoside ? $\xrightarrow{-?}$ Gitalin $\xrightarrow{-2 \text{ digitoxose}}$ Gitaligenin

TABLE 2

CHEMICAL RELATIONSHIPS OF THE GLYCOSIDES OF DIGITALIS LANATA

Lanatoside A $\xrightarrow{-(CH_3COOH \div \text{glucose})}$ Digitoxin $\xrightarrow{-3 \text{ digitoxose}}$ Digitoxigenin .

Lanatoside B $\xrightarrow{-(CH_3COOH \div \text{glucose})}$ Gitoxin $\xrightarrow{-3 \text{ digitoxose}}$ Gitoxigenin

Lanatoside C $\xrightarrow{-(CH_3COOH \div \text{glucose})}$ Digoxin $\xrightarrow{-3 \text{ digitoxose}}$ Digoxigenin

TABLE 3

COMPOSITION OF SPECIMENS OF DIGITALIS PURPUREA FROM VARIOUS SOURCES

Source	Yield from 1 Kg. of Dried Leaf		Ratio of Digitoxin to Gitoxin
	Digitoxin Fraction, Gm.	Gitoxin Fraction, Gm.	
Thuringia..............	0.0005	0.42	0.012
Swiss Jura (cultivated)...	0.15	0.70	0.21
Drug of unknown origin..	0.21	0.70	0.30
Drug of unknown origin..	0.18	0.54	0.33
Harz	0.13	0.26	0.5
U. S. A. (cultivated).....	0.33	0.29	1.14
Drug of unknown origin..	0.27	0.13	2.1
Black Forest............	0.50	0.20	2.5
Vosges................	0.49	0.05	9.8
Vosges................	0.63	0.0	

Data furnished by Dr. E. M. Rothenberger of Sandoz Chemical Works, Inc. from a communication of A. Stoll, Basle, Switzerland.

side present in the same preparation (see Table 1). One can easily see, then, that unless the proportions present are fairly constant, considerable variations in potency may occur, and may occur in man even if the bio-assay does not indicate it.

CARDIAC GLYCOSIDES
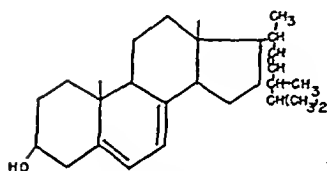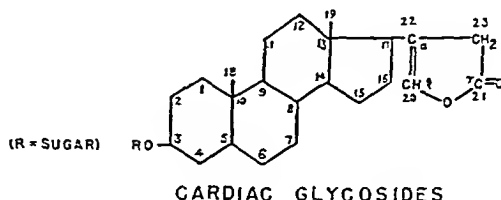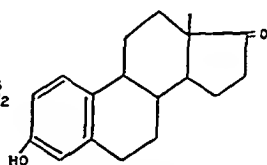
D VITAMINS   ESTROGENS
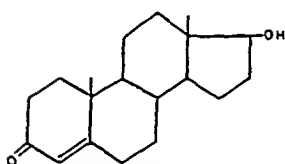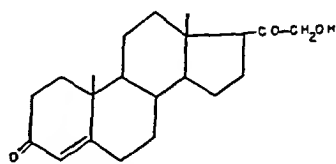
ANDROGENS   CORTICAL HORMONES

Fig. 150.—Chemical relationship of cardiac glycosides to D vitamins, estrogens, androgens and cortical hormones.

Recently a preparation of digitalis powdered leaf was assayed on the cat and was found to be more potent in man than a previous preparation having the same cat assay value. A possible explanation for this may be in the fact that digitoxin, one of the glycosides of digitalis purpurea, is slowly eliminated in contrast to gitoxin and gitalin. In digitalis lanata (Table 2) digitoxin is also found, and is more slowly elim-

TABLE 1

Chemical Relationships of the Glycosides of Digitalis Purpurea

Purpurea glycoside A $\xrightarrow{-\text{glucose}}$ Digitoxin $\xrightarrow{-3\ \text{digitoxose}}$ Digitoxigenin

Purpurea glycoside B $\xrightarrow{-\text{glucose}}$ Gitoxin $\xrightarrow{-3\ \text{digitoxose}}$ Gitoxigenin

Glycoside ? $\xrightarrow{-?}$ Gitalin $\xrightarrow{-2\ \text{digitoxose}}$ Gitaligenin

TABLE 2

Chemical Relationships of the Glycosides of Digitalis Lanata

Lanatoside A $\xrightarrow{-(CH_3COOH + \text{glucose})}$ Digitoxin $\xrightarrow{-3\ \text{digitoxose}}$ Digitoxigenin .

Lanatoside B $\xrightarrow{-(CH_3COOH + \text{glucose})}$ Gitoxin $\xrightarrow{-3\ \text{digitoxose}}$ Gitoxigenin

Lanatoside C $\xrightarrow{-(CH_3COOH + \text{glucose})}$ Digoxin $\xrightarrow{-3\ \text{digitoxose}}$ Digoxigenin

TABLE 3

Composition of Specimens of Digitalis Purpurea from Various Sources

Source	Yield from 1 Kg. of Dried Leaf		Ratio of Digitoxin to Gitoxin
	Digitoxin Fraction, Gm.	Gitoxin Fraction, Gm.	
Thuringia........	0.0005	0.42	0.012
Swiss Jura (cultivated)..	0.15	0.70	0.21
Drug of unknown origin..	0.21	0.70	0.30
Drug of unknown origin..	0.18	0.54	0.33
Harz .. .	0.13	0.26	0.5
U. S. A. (cultivated).	0.33	0.29	1.14
Drug of unknown origin .	0.27	0.13	2.1
Black Forest	0.50	0.20	2.5
Vosges...............	0.49	0.05	9.8
Vosges...............	0.63	0.0	

Data furnished by Dr. E. M. Rothenberger of Sandoz Chemical Works, Inc. from a communication of A. Stoll, Basle, Switzerland.

inated than either of the other two glycosides, digoxin and gitoxin. Variations in digitoxin content must, of necessity, therefore reflect the clinical action of the crude leaf in man.

Before the present war most of the digitalis used in this country came from England and was grown in much the same way and place as it was in the days of Withering. Since the war the chief source of our digitalis leaf is domestic. Recent experiments have shown that variations in amount of sunlight, the calcium and nitrogen content of soil affect materially the relative amounts of the individual glycosides (Table 3), and hence the potency of the crude leaf. This, of course, is quite analogous to variations in the substances found in tobacco dependent upon the growth conditions.

CLINICAL USE OF INDIVIDUAL GLYCOSIDES

It would seem better, therefore, to isolate the individual glycosides and give them as single chemical units by weight, rather than to take a mixture of substances which is standardized on an animal and shows considerable and unpredictable variations. It is noted that, with digitoxin particularly, the rate of elimination is slow and, therefore, a biological assay which extends over a short period of time does not give us a true picture of the potency of the drug. Ideally, the cardiac glycosides should be administered as individuals, rather than as a mixture in the crude digitalis itself. A number of cardiac glycosides are at present available for clinical use (Table 4) and although our knowledge concerning them is not complete, sufficient information has been accumulated to indicate the scope of their clinical usefulness.

Digilanid

The problem of the variability in ratio of the glycosides to each other in digitalis powdered leaf has been surmounted in a preparation known as digilanid, where the glycosides lanatosides A. B and C are isolated and then recombined in a fixed ratio one to another, thus insuring uniform potency. The therapeutic effectiveness and potency of this preparation were studied[6] in twenty-three hospitalized and twenty ambulatory patients and it was found to be a highly satisfactory

TABLE 4

COMMERCIALLY AVAILABLE PREPARATIONS OF PURE DIGITALIS GLYCOSIDES

Product	Manufacturer or Distributor	Glycoside Content
Ouabain	Eli Lilly & Co. Carroll Dunham Smith Pharmacal Co. Hynson, Westcott & Dunning	Crystalline ouabain
K-strophanthin or Strophanthin Kombé	Abbott Laboratories Burroughs Wellcome & Co., Inc.	Amorphous mixture of K-strophanthoside, K-strophanthin-β and cymarin
Strophoside	Sandoz Chemical Works, Inc.	Crystalline K-strophanthoside
Digilanid	Sandoz Chemical Works, Inc.	Crystalline lanatosides A, B and C combined in the approximate ratio of 47 : 16 : 37 respectively
Cedilanid	Sandoz Chemical Works, Inc.	Crystalline lanatoside C
Digitaline Nativelle	E. Fougera & Co.	At least 90% crystalline digitoxin
Digoxin	Burroughs Wellcome & Co., Inc.	Crystalline digoxin
Gitalin (Verodigen)	Rare Chemicals, Inc.	Amorphous gitalin
Urginin	Lederle Laboratories	Scillaren A and B in definite ratio
Thevetin	Eli Lilly & Co.	Crystalline thevetin

preparation, comparable to the powdered leaf in its therapeutic and toxic effects. Digilanid could, therefore, be substituted for the powdered leaf with the same cat assay value with the assurance that the patient would not be rendered severely toxic.

Lanatoside C

Two glycosides, lanatoside C and digoxin, in digitalis lanata have been studied quite extensively. These preparations are very closely related to each other since digoxin is derived

from lanatoside C. They differ, however, pharmacologically since lanatoside C is more rapidly eliminated in the cat than digoxin[7] (Fig. 151).

Following the experimental work of Moe and Visscher[8] on the heart lung preparation, which suggested that lanatoside C had a greater therapeutic range than other cardiac glycosides, Fahr and LaDue[9] studied two hundred and fifty-six patients clinically. They concluded that "Lanatoside C seems definitely less toxic than preparations of digitalis purpurea, and that some patients who cannot tolerate digitalis purpurea

Fig. 151.–Percentage dissipation of the lethal effect of sublethal doses of lanatoside C, digoxin and digoxigenin, with time. (From DeGraff and Lehman, Proc. Soc. Exper. Biol. & Med., *45:* 323, 1940.)

can take lanatoside C in sufficient doses to aid in the relief of their heart failure." Kwit, Gold, and Cattell[10] compared lanatoside C with digitalis leaf in a selected group of sixty-seven ambulatory patients and found that the range between the therapeutic dose and the toxic dose for lanatoside C in man was similar to that of digitalis leaf, roughly 1 as to 2, in contrast to Moe and Visscher of 1 as to 9.

Fahr and LaDue found the maintenance dose to be 1.25 mg. per day (equivalent to 4.5 cat units per day); Kwit, Gold and Cattell, 1.5 mg. to 2.5 mg. per day. Our own re-

sults are nearer to those of Gold, namely 1.4 mg. per day. Since the average maintenance dose of digitalis powdered leaf is 2 cat units per day, the larger amount of lanatoside C necessary to maintain the patient is due either to poor absorption or to rapid elimination. Kwit, Gold and Cattell believe it to be entirely due to poor absorption because five to ten times as much of the drug was needed to digitalize a patient by mouth as intravenously. It is our opinion that these results could be as adequately explained by rapid elimination because in a rapidly eliminated drug the elimination of some of the drug must certainly occur before all of it is absorbed from the gastro-intestinal tract when it is given orally. Referring back to Fig. 151, we see that in the cat lanatoside C is rapidly eliminated. One significant statement in Fahr and LaDue's paper indicates that rapid elimination must be a factor: "In ten cases, nausea and occasional emesis occurred, but, despite these symptoms, the administration of the drug was continued in the same dosage (in most cases 5 tablets per day) and to our surprise both the nausea and the vomiting disappeared." This is, then, a clinical experiment proving the rapid elimination of lanatoside C, confirming in man what we found to be true in the cat.

Lanatoside C (or, as it is known commercially, *Cedilanid*) when given intravenously has a total dose of 1.5 mg. (equivalent to 6 cat units) given over a period of two or three hours. When given by mouth the digitalizing dose is at least 7.5 mg. in divided doses over a period of twenty-four hours. The maintenance dose averages 1.5 mg. a day. Because of its rapid elimination, it is difficult to render a patient toxic, or if he becomes toxic, the duration of toxic symptoms is short. On the other hand, it is more difficult to keep a patient on a proper therapeutic level of digitalization.

Digoxin

Digoxin, closely related to lanatoside C, is also more rapidly eliminated than some other glycosides, for instance, digitoxin, but not nearly as rapidly as lanatoside C. In twenty-six patients the therapeutic digitalizing dose by mouth was found to be between 2 and 5 mg. The toxic dose was roughly

from lanatoside C. They differ, however, pharmacologically since lanatoside C is more rapidly eliminated in the cat than digoxin[7] (Fig. 151).

Following the experimental work of Moe and Visscher[8] on the heart lung preparation, which suggested that lanatoside C had a greater therapeutic range than other cardiac glycosides, Fahr and LaDue[9] studied two hundred and fifty-six patients clinically. They concluded that "Lanatoside C seems definitely less toxic than preparations of digitalis purpurea, and that some patients who cannot tolerate digitalis purpurea

Fig. 151.—Percentage dissipation of the lethal effect of sublethal doses of lanatoside C, digoxin and digoxigenin, with time. (From DeGraff and Lehman, Proc. Soc. Exper. Biol. & Med., 45: 323, 1940.)

can take lanatoside C in sufficient doses to aid in the relief of their heart failure." Kwit, Gold, and Cattell[10] compared lanatoside C with digitalis leaf in a selected group of sixty-seven ambulatory patients and found that the range between the therapeutic dose and the toxic dose for lanatoside C in man was similar to that of digitalis leaf, roughly 1 as to 2, in contrast to Moe and Visscher of 1 as to 9.

Fahr and LaDue found the maintenance dose to be 1.25 mg. per day (equivalent to 4.5 cat units per day); Kwit, Gold and Cattell, 1.5 mg. to 2.5 mg. per day. Our own re-

TABLE 5

Summary of Doses of Digitaline Nativelle in a Group of Thirty-one Ambulatory Patients

Daily Dose		Number of Patients			
Mg.	Trials	Well Maintained	Fairly Well Maintained	Developed Increased Congestive Heart Failure	Developed Toxicity
0.05........	8	7	0	1	0
0.105.......	21	11	1	7	2
0.21.... ...	28	16	3	1	8
0.315.......	22	9	2	0	11
0.42........	14	5	1	0	8
0.535.......	4	3	0	0	1
0.63........	3	2	0	0	1
0.7.........	1	1	0	0	0

TABLE 6

Ratio between Minimal Maintenance Dose and Toxic Dose for Digitoxin (Digitaline Nativelle)

Number of Patients	Minimal Maintenance Dose	Toxic Dose
2	1	$1\frac{1}{3}$
4	1	$1\frac{1}{2}$
5	1	2
1	1	$2\frac{1}{2}$
5	1	4
1	1	8

Digitaline Nativelle is 0.1 to 0.2 mg., a figure similar to that noted by Gold and co-workers. Table 6 shows the range between minimal maintenance dose and the toxic dose in

twice this amount, showing that the therapeutic range was like digitalis powdered leaf. In terms of cat units the dosage closely paralleled that of digitalis powdered leaf. The maintenance dose, however, reflected the more rapid elimination of digoxin as compared with digitalis powdered leaf in that the average daily maintenance dose was 0.75 mg. However, when compared with lanatoside C, the elimination is much slower.

Digitoxin

Digitoxin was isolated by Nativelle[11] in 1869, and for many years was marketed in France as Digitaline Nativelle. Later Merck in Germany marketed digitoxin as Digitoxin (Merck). Both of these preparations were available in this country before the War. The commercial preparation of digitoxin now available is known as *Digitaline Nativelle* and probably consists of at least 90 per cent digitoxin. The potency and effectiveness of this preparation has recently been reported by Gold and associates.[12] These investigators showed that the cat method of assay on the purified cardiac glycosides was not transferable to man. They found, for instance, that in terms of cat units, six times as much digitalis powdered leaf as Digitaline Nativelle was necessary to digitalize or maintain a patient.

The digitalizing dose of digitoxin is 1 to 1.25 mg. by oral administration. The toxic dose is roughly twice this amount, indicating again a similarity in this regard to other cardiac glycosides. We have treated thirty-one patients with Digitaline Nativelle; twenty-three of these patients had auricular fibrillation; eight, regular sinus rhythm. All these patients were ambulatory and had been previously maintained on digitalis. They were placed on a given dose of digitoxin and were left on this dose at least eight weeks unless they showed signs of toxicity or increasing signs of heart failure. At the end of this time, the dose was either increased or decreased for another period of observation. Trials were made on these patients at various dose levels and the results are summarized in Table 5. It will be noted that considerable individual variability occurs. However, the average maintenance dose with

Ouabain is crystalline and therefore uniform. K-strophanthin is amorphous and varies in composition from lot to lot. Ouabain, therefore, is to be preferred. Both G-strophanthin and K-strophanthin and their derivatives are poorly absorbed and, therefore, are best given intravenously. They are also rapidly eliminated. In describing a new method of digitalization[15] we made use of this fact by combining the intravenous injection of ouabain with the simultaneous administration of digitalis powdered leaf by mouth.

In Table 7 the commercially available glycosides and their therapeutic, toxic and maintenance doses are listed.

CONCLUSION

Although there is still a great deal of basic work, both pharmacological and clinical, to be done on the cardiac glycosides, we can safely predict that in the not too distant future all of our digitalis therapy will be given as glycosides. It is evident that although a similarity in chemical structure and therapeutic effect exists between the cardiac glycosides, differences are still great enough so that one single glycoside will probably not suffice for all clinical needs. Just as we need barbituric acid derivatives that are short and long acting, so do we need at different times glycosides that are rapidly eliminated and at other times those which are slowly eliminated. As these drugs can now be studied more intimately in man as well as in animals, minor differences will be noted and catalogued, just as have been done for other series of chemical substances. The physician using these drugs is, therefore, close to the investigator, and it is his duty to make careful and accurate observations every time he uses one of these potent cardiac glycosides.

BIBLIOGRAPHY

1. Withering, W.: An Account of the Foxglove and Some of Its Medicinal Uses: With Practical Remarks on Dropsy and Other Diseases. 1785.

eighteen patients in whom both doses could be established. In other words, 61 per cent of the patients became toxic when the minimal maintenance dose was doubled.

Digitoxin is very slowly eliminated, and toxicity from this glycoside may persist, therefore, for a long time. We have

TABLE 7

Therapeutic, Toxic and Maintenance Doses of Commercially Available Glycosides

Preparation	Therapeutic Dose		Toxic Dose		Maintenance Dose	
	By Weight	Units in Terms of Cat Assay	By Weight	Units in Terms of Cat Assay	By Weight	Units in Terms of Cat Assay
Digitalis leaf	1 5–2 0 gm.	15–20	2 0–3 0 gm.	20–30	0 1–0 2 gm	1–2
Digilanid (Crystalline lanatosides A, B and C in a definite ratio)	3 3–8 91 mg. (6 6 mg)	10–27 (20	4 29–16 33 mg (10 mg	13–51 (30	0 33–0 65 mg	1–2
Digoxin	2 0–6 0 mg. (3 75 mg)	10–31 (19.5	2 0–12 0 mg (6 mg)	10–62 (31	0 5–1 0 mg.	2 5–5
Lanatoside C Gold 3			6 25–13 mg	25–52	1 5–2 5 mg	6–10
Fahr	6 25 mg.	25			0 25–1 25 mg	1–5
Digitoxin (Digitaline Nativelle)	1 26–2 52 mg (1 66 mg)	3–6 (4	1 66–5 85 mg (3.57 mg)	4–14 (8.5	0 05–0 21 mg	1–1½
Urginin (Scillaren A and B in a definite ratio, Chamberlin and Levy 4	6 5–14 mg (9 mg)	26–56 (36	18 mg (45)	72 (45)	0 5–2 0 mg	2–4
Ouabain (iv	0 5–1 0 mg (0 7 mg)	5–10 (7)	0 7–1 3 mg (0 9 mg)	7–15 (9		
G'lala	4–8 mg	5–10		. .	0 25–0 50 mg.	0 5–0 6

had one patient who continued to have signs of toxicity for a week. Therefore, patients who are receiving digitoxin must be under fairly close supervision.

Ouabain and K-strophanthin

Strophanthin is used in two forms, Gratus strophanthin, in the form of the glycoside Ouabain, and Kombé strophanthin.

THE USE OF FLUORESCEIN TO DETERMINE THE ADEQUACY OF THE CIRCULATION*

KURT LANGE, M.D.†

and

LINN J. BOYD, M.D., F.A.C.P.‡

THE practical determination of the presence or absence of an adequate circulation in various parts of the body is a common and urgent problem often involving a serious decision. Such questions constantly arise in several divisions of medicine. For example, it is vital for the surgeon to know immediately whether an adequate blood supply is available to a portion of the intestine after an incarceration has been released. Inability to answer this question correctly and rapidly means that a resection must be performed at times although it may unnecessarily complicate the operative procedure, and increase the hazard. Often it is dangerous to ligate vessels when large tumors must be resected; severance of blood supply may leave dependent parts of the intestine without an available blood supply. A somewhat similar situation exists in the field of peripheral vascular diseases; the choice of a site for amputation could be greatly simplified if the borderline between adequate and inadequate blood supply could be determined. In the field of internal medicine, fluorescein offers an objective method for ascertaining the circulation time and facilitates the diagnosis of circulatory failure, hyper- or hypothyroidism and congenital cardiovascular lesions. The primary purpose of the following remarks is to direct attention to these possibilities.

*From the Department of Medicine, the New York Medical College; Flower and Fifth Avenue Hospitals (Metropolitan Hospital Service).

† Instructor in Medicine, New York Medical College, Flower and Fifth Avenue Hospitals; Assistant Visiting Physician, Metropolitan Hospital.

‡ Professor of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals; Visiting Physician and Director of the Service, Metropolitan Hospital.

2. Houghton, E. M.: The Pharmacological Assay of the Heart Tonics. J.A.M.A., *31:* 959, 1898.

3. Hatcher, R. A. and Brody, J. G.: The Biological Standardization of Drugs. Am. J. Pharm., *82:* 360, 1910.

4. Gold, H., Cattell, M., Kwit, N. T. and Kramer, M.: The Relative Activity of Digitalis Preparations in the Frog, the Cat and Man, and Its Bearing on the Problem of Bio-assay and So-called Deterioration. J. Pharm. & Exper. Therap., *73:* 212, 1941.

5. DeGraff, A. C., Paff, G. H. and Lehman, R. A.: The Quantitative Effect of Fifteen Chemically Related Glycosides and Genins on the Embryonic Chick Heart. J. Pharm. & Exper. Therap., *72:* 211, 1941.

6. Batterman, R. C., Holman, D. V. and DeGraff, A. C.: The Therapeutic Effectiveness and Potency of Digilanid in the Treatment of Congestive Heart Failure. Ann. Int. Med., *14:* 2058, 1941.

7. DeGraff, A. C. and Lehman, R. A.: Fate of the Lethal Effect of Sublethal Doses of Lanatoside C, Digoxin and Digoxigenin. Proc. Soc. Exper. Biol. & Med., *45:* 323, 1940.

8. Moe, G. K. and Visscher, M. B.: Studies on the Native Glucosides of Digitalis Lanata with Particular Reference to Their Effect Upon Cardiac Efficiency and Their Toxicity. J. Pharm. & Exper. Therap., *64:* 65, 1938.

9. Fahr, G. and LaDue, J.: A Preliminary Investigation of the Therapeutic Value of Lanatoside C (Digilanid C). Am. Heart J., *21:* 135, 1941.

10. Kwit, N. T., Gold, H. and Cattell, M.: Studies on Purified Digitalis Glucosides II, Potency and Dosage of Lanatoside C in Man. J. Pharm. & Exper. Therap., *70:* 254, 1940.

11. Nativelle, C. A.: J. Pharmacodynamie, *9:* 255, 1869.

12. Gold, H., Kwit, N. T. and Cattell, M.: Studies on Purified Glucosides I, Potency and Dosage of "Digitaline Nativelle" by Oral Administration in Man. J. Pharm. & Exper. Therap., *69:* 177, 1940.

13. Batterman, R. C., Rose, O. A. and DeGraff, A. C.: The Combined Use of Ouabain and Digitalis in the Treatment of Congestive Heart Failure. Am. Heart J., *20:* 443, 1940.

14. Chamberlain, F. L. and Levy, R. L.: Clinical Study of a Preparation of Squill (Urginin) in the Treatment of Myocardial Insufficiency. Am. Heart J., *14:* 268, 1937.

CLINICAL AND EXPERIMENTAL OBSERVATIONS

Adequacy of Intestinal Blood Supply after Release of Incarceration

CASE I. INCARCERATED HERNIA.—K. W. was admitted to Metropolitan Hospital on November 11, 1941; two days earlier she had experienced sudden sharp pain in the lower right quadrant. The pain was intermittent and recurred every few minutes. At the time of hospitalization it had diminished in intensity. She had not vomited and had passed a poorly formed stool on the day before admission. The pain started after a paroxysm of coughing.

The past history was uninformative except for an operation for an incarcerated hernia on the right side twenty years ago.

The examination revealed a seventy-three-year-old female without pathologic findings save for the abdomen. There was marked direct and rebound tenderness in the right lower quadrant, but no muscle spasm. An elastic mass was palpable about 1 inch above the right inguinal ligament. This mass did not increase in size with slight coughing. No attempt was made to reduce it.

One per cent novocain was infiltrated locally by a staff surgeon and an 8 cm. incision made. The round ligament was located and dissected free from the floor of the canal. A hard palpable mass was palpated extending along the round ligament. The peritoneum was opened in the floor of the inguinal canal and the contents of the hernia reduced from within. It consisted of incarcerated omentum.

Fluorescein (2½ cm. of a 5 per cent solution) was injected intravenously and the room was darkened. The omentum whose viability was questioned was exposed under ultraviolet light. There was no emission of fluorescence from the suspected area, consequently the circulation was considered inadequate and this section of the omentum was resected. The appendix was also exposed to the ultraviolet light and showed full and intense fluorescence of all its parts. Uneventful recovery followed.

This particular case is introduced simply to illustrate the method briefly and to suggest its possibilities.

Studies have also been made with the appearance of various organs after the injection of fluorescein. Fluorescein stains the serum and leaves the corpuscles unstained. Certain cell elements readily absorb the dye and excrete it again. If a definite section of tissue containing a small artery and vein

Nature of Fluorescein.—Fluorescein is resorcinolphthalein. It is readily available, inexpensive and nontoxic. Strauss[1] administered it orally in doses of 1 gm. to test renal function without noting any deleterious effects; as much as 6 gm. has been given by mouth to stain certain parts of the eye; no untoward symptoms follow although the skin may be stained yellow for twelve to thirty hours under those circumstances. Fluorescein is excreted unchanged in the urine.

When examining the physical properties of fluorescein for possible use as a vital stain, we found it emits its strongest fluorescence when the source of light has a wave length of 3600 to 4000 Angstrom units. This is the region of long wave ultraviolet. This purple light causes fluorescein to emit a gold to green fluorescence depending upon the hydrogen ion concentration of the media in which the action takes place. In an acid solution the emitted light is yellow, while in an alkaline solution it is dull green.

Technic of Test.—A simple mercury vapor lamp similar to that employed by mineralogists in fluorescence microscopy or in vitamin research is provided with a glass filter which absorbs most of the visible rays. The light beam is directed against the lips of the patient. The examination should take place, if possible, in a slightly darkened room. Two to four cubic centimeters of a 5 per cent fluorescein solution to which 5 per cent of sodium bicarbonate has been added are injected rapidly into the antecubital vein. After the circulation time has passed, the part under observation (lips, tongue, gum, eyelids) suddenly acquires a greenish-yellow appearance. This end-point is sharply defined. When several observers are present, they rarely disagree more than one second on the moment it appears. If no subsequent examination is intended within a short period, larger doses may be employed for demonstration purposes. If the test is to be repeated, the amount injected should not exceed 2 cc. and usually the effect has diminished sufficiently within fifteen minutes to permit a second examination with a clear-cut result. We have employed up to 12 cc. of the solution in a single intravenous injection and up to 15 cc. within two hours without any ill effects.

sections do not stain homogeneously like uninjured parts, probably owing to capillary spasm or thrombosis. Naturally, further experience will be required to determine the degree of staining necessary before it can be definitely said that necrosis will not occur. These refinements must be left to surgeons who have more opportunity to study this problem than internists. However, many points can readily be ascertained. For example, in two experiments with clamps the circulation was not restored after application of Payen clamps for twenty minutes.

In eight animals major branches of the superior and inferior mesenteric artery were obstructed by clamps whose blades were covered with rubber. A situation similar to *mesenteric embolism* was produced, and the events studied after the intravenous injection of fluorescein. Illumination revealed that many parts of the small intestine were unaffected, since an excellent collateral circulation exists. It was necessary to clamp the main branches at their origin from the superior mesenteric artery to obtain total failure of fluorescence in the dependent portions of the bowel. A wedge-shaped area, very distinct amid the green fluorescence is produced with its tip toward the points of vascular occlusion when the mesentery is unfolded. The large bowel seems to possess fewer collaterals since clamping, even of small arteries, nearly always caused a total or subtotal loss of fluorescence after intravenous injection of the dye. If the clamping is discontinued after a short time, fluorescence immediately reappears.

Since the human intestine readily yields an intense fluorescence after the injection of 3 to 4 cc. of a 5 per cent solution, the results obtained in animal experiments can be transferred to human surgery and the method may offer considerable assistance in suspected beginning gangrene of the bowel and in mesenteric infarction.

Adequacy of Blood Supply in Peripheral Vascular Obstruction

CASE II. DIABETIC GANGRENE OF LEFT FOOT.—B. C. was admitted August 7, 1941, for a lesion on the left foot. One week previously she had noticed a dark spot on the sole of this foot which soon broke down and extended. The foot was dressed at a clinic but the area enlarged and she became unable to walk. Her diet was rather well controlled and she had been taking 20 units of protamine zinc insulin each day.

On admission there was a dry lesion on the left sole approximately the size of a quarter; this necrotic area was surrounded by a discolored ring approximately twice its size. On August

is observed with the aid of a low power microscope after intravenous injection, one readily can watch the stain enter the artery, pass the capillaries, stain the surrounding tissue and return through the vein. The time elapsing between the appearance of the stain in the artery and its appearance in the vein represents the local circulation time in this district. Moreover, the method offers a means of determining the influence of drugs on the peripheral resistance in a given area.

EXPERIMENTAL STUDIES.—After intravenous injection of fluorescein, the human and animal intestine is deeply stained owing to its rich blood supply. For experimental purposes, surgical conditions were created in the intestines of twelve rabbits in that the blood supply was partly or completely obstructed from parts of the bowel.

No. of Animals	Duration of Incarceration (Minutes)	Restoration of Circulation, Complete	Restoration of Circulation, Partial
1	60	+	
2	150	+	
1	220	+	
1	220	~	Patchy fluorescence.
2	255	~	No restitution after 300 minutes

In seven animals a loop of small intestine was slipped through a narrow rubber band so that the blood supply was entirely interrupted. After intravenous injection of 0.2 cc. of a 5 per cent fluorescein solution, all parts of the intestine emitted a golden-green light under the influence of the ultraviolet lamp except the incarcerated part which remained purple. The incarceration was released after different intervals of time and fluorescein was reinjected. It could easily be demonstrated how important the time factor is on the restitution of circulation of a previously incarcerated segment. These results are summarized in the tabulation.

These results indicate, under the conditions of the experiment, that four hours of interruption of the bowel circulation are required to produce a lesion with lasting local failure of the circulation. Incarcerations of a shorter duration, upon release, immediately permit the emission of typical light after an injection of fluorescein. However, in these cases the incarcerated

The arm-tongue time can be estimated by the development of a bitter taste after the injection of sodium dehydrocholate.[3] Saccharin[4] has been utilized for the same purpose, the appearance of a sweet taste constituting the end-point. Magnesium sulfate[5] and calcium preparations depend upon the development of a sensation of heat. The major objection to these substances is that the end-points are subjective. Death[6] has been reported after the use of ether and saccharin to determine the so-called lung circulation time. The use of calcium may be extremely dangerous in digitalized patients.[7] Sodium cyanide may cause syncope and respiratory arrest.[8] Other agents produce venous thrombosis at the point of injection. Lobeline[9] fails to evoke a response in some patients.

Among the so-called objective methods a few deserve mention. The inhalation of carbon dioxide[10] provides a lung-brain time; while objective, it requires considerable equipment and can scarcely be performed in children or unconscious subjects. The employment of radioactive substances in one arm and their detection in the opposite extremity by means of a sensitive electroscope[11] involves a large amount of apparatus which cannot be brought to the bedside. The more recent suggestion to use histamine[12] and to watch for the appearance of a facial flush seemed rational. Unfortunately, we like others have had unpleasant accidents with it in patients with bronchitis, bronchial asthma, pulmonary emphysema, and severe myocardial damage.

Koch[13] injected fluorescein into one arm vein and observed the appearance of fluorescent serum in blood collected from the opposite arm at 5-second intervals. The procedure is complicated and not very accurate. Subsequently Hirth and Ellinger[14] demonstrated the presence of fluorescein in the kidney of a frog under a low power microscope after the dye had been injected into a lymph sac. Stimulated by these observations we tried to demonstrate directly the presence of fluorescein in the tissues of man and animals after the injection of the substance into the antecubital vein.

We do not intend to describe at this time the detailed results in the 256 cases examined. Eighty-nine normal adults above the age of twenty had an average arm-lip time of 17.1 seconds. The lowest and highest values were 15 and 20 seconds respectively. All patients were examined in the recumbent position after 15 minutes rest. The amount of dye injected in all was 2–4 cc. Special care was taken to eliminate

13 a femoral vein ligation and débridement of the infected area on the foot was done in the surgical division. The posterior tibial pulse returned after these procedures. By October 13 the ulcerated area had practically healed; a moist area about 0.25 cm. in diameter remained.

On November 15, 5 cc. of 5 per cent of fluorescein was injected intravenously, the room was darkened, and the ultraviolet light directed at first to the dorsum of the foot up to the lower half of the tibia. Clear fluorescence of the skin was noted over the entire leg up to a line 2 cm. above the ankle. Below this there was a wedge-shaped area which extended down to and including the middle toe, indicating a considerable reduction of the blood supply in this area. The sides of the foot yielded good fluorescence.

The method permitted the diagnosis of a markedly impaired circulation on the dorsum of the left foot including the middle toe.

EXPERIMENTAL STUDIES.—The skin of our experimental animals (rabbits) does not become fluorescent as readily as the mucous membranes and the intestines do. The stratum corneum seems to absorb much of the ultraviolet rays so that only small amounts reach the capillaries to excite fluorescence there. However, four to ten minutes after the injection of the dye, the cells themselves are sufficiently stained to yield a more or less intense fluorescence. Old scar tissue, on the contrary, remains purple while the surrounding skin is yellow-green. We have ligated the left iliac artery below the bifurcation and have seen the entire skin of the animal emit an intense greenish light four minutes after the injection of 2 cc. of fluorescein intravenously, while the skin of the left hind leg remained purple; the line of demarcation is very sharp. Further experiments are in progress, but sufficient observations have accumulated to merit the attention of other observers, for this field seems most promising.

Circulation Time

We possess much more evidence in this direction[2] than in the preceding applications which may be of greater interest to surgeons than to internists. It is generally known that a wide variety of substances have been employed to determine the circulation time and it seems probable that the multiplicity of methods is indicative of the dissatisfaction with most of them.

The arm-tongue time can be estimated by the development of a bitter taste after the injection of sodium dehydrocholate.[3] Saccharin[4] has been utilized for the same purpose, the appearance of a sweet taste constituting the end-point. Magnesium sulfate[5] and calcium preparations depend upon the development of a sensation of heat. The major objection to these substances is that the end-points are subjective. Death[6] has been reported after the use of ether and saccharin to determine the so-called lung circulation time. The use of calcium may be extremely dangerous in digitalized patients.[7] Sodium cyanide may cause syncope and respiratory arrest.[8] Other agents produce venous thrombosis at the point of injection. Lobeline[9] fails to evoke a response in some patients.

Among the so-called objective methods a few deserve mention. The inhalation of carbon dioxide[10] provides a lung-brain time; while objective, it requires considerable equipment and can scarcely be performed in children or unconscious subjects. The employment of radioactive substances in one arm and their detection in the opposite extremity by means of a sensitive electroscope[11] involves a large amount of apparatus which cannot be brought to the bedside. The more recent suggestion to use histamine[12] and to watch for the appearance of a facial flush seemed rational. Unfortunately, we like others have had unpleasant accidents with it in patients with bronchitis, bronchial asthma, pulmonary emphysema, and severe myocardial damage.

Koch[13] injected fluorescein into one arm vein and observed the appearance of fluorescent serum in blood collected from the opposite arm at 5-second intervals. The procedure is complicated and not very accurate. Subsequently Hirth and Ellinger[14] demonstrated the presence of fluorescein in the kidney of a frog under a low power microscope after the dye had been injected into a lymph sac. Stimulated by these observations we tried to demonstrate directly the presence of fluorescein in the tissues of man and animals after the injection of the substance into the antecubital vein.

We do not intend to describe at this time the detailed results in the 256 cases examined. Eighty-nine normal adults above the age of twenty had an average arm-lip time of 17.1 seconds. The lowest and highest values were 15 and 20 seconds respectively. All patients were examined in the recumbent position after 15 minutes rest. The amount of dye injected in all was 2–4 cc. Special care was taken to eliminate

any individual who presented any sign of hyperthyroidism despite a normal metabolic rate.

The direct fluorescein method was employed to determine the circulation time in seventy-eight patients with cardiac failure or beginning cardiac failure. The range of circulation time in this group was 20 to 68 seconds, with an average of 39 seconds. Eight patients did not show a prolonged circulation time despite apparent failure. In severe failure we usually increased the amount of dye to 3–4 cc. to compensate for the dilution resulting from the slow circulation time. In some cases the lips were extremely dry and furred with a brown coating, which prevented the appearance of a clear end-point.

Day of Hospitalization	Treatment	Pulse Rate	Basal Metabolic Rate	Circulation Time (Seconds)
3	Bed rest	116	+51	7
7	Bed rest	104	+48	8
17	Lugol's 9 days	90	+32	10
24	Lugol's 16 days	90	+19	10
25	Subtotal Thyroidectomy			
32	Bed rest	96	+ 7	10
46	Out of bed	90	+ 4	11
60	At home	86	+ 4	16
90	At home	90	+ 6	16

In these cases the tongue or the mucous membrane of the mouth could be used.

Thirty-six cases of hyperthyroidism were examined; the average circulation time was 10.6 seconds. None of them showed a circulation time of more than 14 seconds and the shortest time was 7 seconds. The circulation time is a very sensitive test for *hyperthyroidism* and this decrease persists to some extent after the basal metabolic rate has returned to normal under treatment. It often requires several weeks after a subtotal thyroidectomy before the circulation time returns to normal.

This point is demonstrated by the above figures which were obtained in a young woman twenty-seven years of age.

Nine cases of hypothyroidism were followed continuously

and the circulation time was found slightly or markedly prolonged in all except one. The average in this group amounted to 26 seconds.

SUMMARY

1. Fluorescein is nontoxic, inexpensive, readily available and devoid of untoward effects even when used in large doses. Its presence in the tissues can be easily determined by its fluorescence under ultraviolet light. Accordingly, a method is available for the determination of the general or local circulation time, and for establishing the presence and adequacy of local circulation. In regard to the first it is an objective method devoid of the defects of other procedures; in respect to the second it seems to possess greater delicacy and wider utility than the injection of radiopaque substances whose field of application is naturally rather limited.

2. The new objective method for determining the circulation time yields the following values: Normal adults range from 15 to 20 seconds with an average of 17.1 seconds in eighty-nine patients; in cardiac failure the time varies from 20 to 68 seconds (average 39) although 10 per cent of seventy-eight patients had a normal reading; hyperthyroidism was always associated with a shortened circulation time, 7 to 14 seconds (average 10.6 seconds in thirty-six cases). Neither Lugol's solution nor operation immediately induce a reversion to normal despite a favorable influence on the basal metabolic rate by these measures. Eight of nine cases of hypothyroidism showed a prolonged circulation time of 21 to 34 seconds (average 26 seconds).

3. Although the dye can be used to determine the circulation time in all types of experimental animals without recourse to anesthesia and hence permits studies of the permeability of vessels under the influence of drugs, this has not been discussed in this clinical paper.

4. The intestine of experimental animals and man shows an intense fluorescence after the intravenous injection of fluorescein and ultraviolet illumination of the intestine. Incarcerated portions of the bowel do not give this emission and the adequacy of the blood supply to the viscus, after liberation from incarceration, can be immediately ascertained. Clamping of the mesenteric arteries may cause infarction which can be

any individual who presented any sign of hyperthyroidism despite a normal metabolic rate.

The direct fluorescein method was employed to determine the circulation time in seventy-eight patients with cardiac failure or beginning cardiac failure. The range of circulation time in this group was 20 to 68 seconds, with an average of 39 seconds. Eight patients did not show a prolonged circulation time despite apparent failure. In severe failure we usually increased the amount of dye to 3–4 cc. to compensate for the dilution resulting from the slow circulation time. In some cases the lips were extremely dry and furred with a brown coating, which prevented the appearance of a clear end-point.

Day of Hospitalization	Treatment	Pulse Rate	Basal Metabolic Rate	Circulation Time (Seconds)
3	Bed rest	116	+51	7
7	Bed rest	104	+48	8
17	Lugol's 9 days	90	+32	10
24	Lugol's 16 days	90	+19	10
25	Subtotal Thyroidectomy			
32	Bed rest	96	+ 7	10
46	Out of bed	90	+ 4	11
69	At home	86	+ 4	16
90	At home	90	+ 6	16

In these cases the tongue or the mucous membrane of the mouth could be used.

Thirty-six cases of hyperthyroidism were examined; the average circulation time was 10.6 seconds. None of them showed a circulation time of more than 14 seconds and the shortest time was 7 seconds. The circulation time is a very sensitive test for *hyperthyroidism* and this decrease persists to some extent after the basal metabolic rate has returned to normal under treatment. It often requires several weeks after a subtotal thyroidectomy before the circulation time returns to normal.

This point is demonstrated by the above figures which were obtained in a young woman twenty-seven years of age.

Nine cases of hypothyroidism were followed continuously

RECENT ADVANCES IN OPHTHALMOLOGY OF GENERAL INTEREST*

BRITTAIN FORD PAYNE, M.D., F.A.C.S.†

THE progress of ophthalmology in the past few years compares favorably with that of all other branches of medicine. At least two new surgical procedures are being developed for the cure of hopeless blindness resulting from corneal scars and retinal detachments. The introduction of sulfanilamide and its derivatives has contributed much to the alleviation of trachoma and Neisserian infections. Certain vitamin preparations have proved their worth in various pathologic involvements of the eye. Aside from the widely publicized measures just mentioned, there has been steady progress in the study of the eye in relation to general disease. There is a new appreciation of functional testing and the application of certain measures to alleviate eyestrain and improve reading ability. So many articles have been written about corneal grafts, retinal detachment operations, sulfanilamide and vitamins that only a few paragraphs will be devoted to them. The tendency of most textbooks to avoid common eye lesions, whether associated with trauma, general or local disease, calls for a review of some of these conditions.

TRAUMATIC LESIONS AND THEIR CARE

Foreign Bodies

The most common traumatic lesion of the eye is the embedding of a foreign body on the cornea or tarsus. If the foreign body is on the tarsus, it may be removed with an applicator by everting the eyelid. If it is embedded in the cornea,

demonstrated by the absence of fluorescence in the area affected. The importance of these observations hardly requires emphasis.

5. Finally the skin can also be made fluorescent and the portions of the extremities not supplied by blood remain dark rather than fluorescent. The application of this diagnostic aid in peripheral vascular disease has been shown by an illustrative case of diabetic gangrene.

BIBLIOGRAPHY

1. Strauss, H.: Fluorescein als Indikator für die Nierenfunktion. Berl. klin. Wchnschr., 50: 2226, 1913.
2. Wollheim, E. and Lange, K.: Die Kreislaufzeit und ihre Beziehung zu anderen Kreislaufgrössen. Verhandl. d. deutsch. Gesellsch. f. inn. Med., 43: 134–140, 1931.
3. Tarr, L., Oppenheimer, B. S. and Sager, R. V.: Circulation Time in Various Clinical Conditions Determined by the Use of Dehydrocholate. Am. Heart J., 8: 766–786 (Aug.) 1933.
4. Fishberg, A. M., Hitzig, W. M. and King, F. H.: Measurement of the Circulation Time with Saccharin. Proc. Soc. Exper. Biol. & Med., 30: 651–652 (Feb.) 1933.
5. Bernstein, M. and Simkins, S.: The Use of Magnesium Sulfate in the Measurement of Circulation Time. Am. Heart J., 17: 218–237 (Feb.) 1939.
6. Leinoff, H. D.: Complications Following Use of Saccharin and Ether As a Circulation Time Test. J.A.M.A., 105: 1759 (Nov. 30) 1935.
7. Bower, J. O. and Mengle, H. A. K.: Additive Effect of Calcium and Digitalis; Warning, with Report of Two Deaths. J.A.M.A., 106: 1151–1153 (April 4) 1936.
8. Loevenhart, A. S., Lorenz, W. F., Martin, H. G. and Malone, J. Y.: Stimulation of the Respiration by Sodium Cyanid and Its Clinical Application. Arch. Int. Med., 21: 109–129 (Jan.) 1918.
9. Stanojevic, L.: Die Bestimmung der Kreislaufzeit mit Lobelin. Ztschr. f. Kreislaufforsch., 30: 521–528 (July) 1938.
10. Bornstein, A.: Ueber die Messung der Kreislaufzeit in der Klinik. Verhandl. d. deutsch. Kongr. f. inn. Med., 29: 457–460, 1912.
11. Blumgart, H. L. and Yens, O. C.: Studies on the Velocity of Blood Flow. J. Clin. Invest., 4: 1–13 (April) 1927.
12. Weiss, S., Robb, G. P. and Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease as Measured by the Effect of Histamine on the Minute Vessels. Am. Heart J., 4: 664–691 (Aug.) 1929.
13. Koch, E.: Die Stromgeschwindigkeit des Blutes. Ein Beitrag zur Arbeitsprüfung des Kreislaufes. Deutsches Arch. f. klin. Med., 140: 39–66 (July) 1922.
14. Ellinger, P. and Hirt, A.: Mikroskopische Untersuchungen an lebenden Organen: zur Funktion der Froschniere. Arch. f. exper. Path. u. Pharmakol., 145: 193–210, 1929.

severe contusions. Considerable experience is necessary to determine the type of treatment to be followed in these cases, and frequently an eye is lost in spite of most skillful attention.

Minor blows on the eyeball may cause some redness, photophobia and mild iritis. The eyelid may be swollen and careful examination by means of fluorescein may show a corneal abrasion. If the cornea shows a stain after the instillation of fluorescein, followed by irrigations with normal saline solution, it is almost imperative to apply an antiseptic ointment and close the eye with a snug dressing. The use of a mydriatic is debatable. If it is definitely determined that the intraocular tension is normal and there is little or no hemorrhage in the anterior chamber, the use of a 2 per cent solution of homatropine may relieve most of the pain and hasten the recovery. If the injured eye shows evidence of glaucoma or hardening, any and all mydriatics are contraindicated.

The presence of severe iritis, massive hemorrhage into the anterior chamber, secondary glaucoma, or detachment of the retina usually requires hospitalization, and every attempt should be made to keep the patient in bed with the eyes at absolute rest. Foreign protein therapy for traumatic iritis has been advocated by some clinicians and criticized by others; and in many cases, the application of heat may cause a dangerous hemorrhage to be followed by glaucoma and loss of sight. Cool applications, sedatives, complete rest and guarded use of foreign proteins may constitute the treatment for iritis or hemorrhage into the anterior chamber. Glaucoma as a result of trauma frequently causes the loss of sight and the eye may have to be removed because of intractable pain. Retinal detachments require hospitalization and operation by an experienced surgeon after sufficient time has been given for possible spontaneous reattachment, which is rare.

COMMON INFECTIONS OF THE EYELIDS

The two most common infections of the eyelids are the *hordeolum* and the *chalazion*. The hordeolum is external and usually occurs around a cilium and cultures reveal the Staphylococcus aureus organism. The chalazion is internal and confined to the meibomian glands. Both may be extremely pain-

considerable dexterity, sufficient light, local anesthesia and proper instruments are needed to insure clean removal with the least possible damage to adjacent tissues. After a foreign body is removed, a drop of 2 per cent homatropine solution should be instilled to relax the iris and ciliary body. An antiseptic ointment should be used and the eye should be closed with a dressing. If the crater left by the foreign body is superficial, the dressing may be removed on the following day but it is often necessary to keep the eye closed for several days. Deeply embedded foreign bodies often cause scars and there is always danger of infection which may alter the treatment entirely. Intra-ocular foreign bodies do not fall within the scope of this paper and should receive the immediate attention of an ophthalmic surgeon.

Abrasions of the Cornea

Abrasions of the cornea are difficult to see but are very painful. The instillation of a drop of 2 per cent fluorescein, followed by copious irrigations of normal saline solution, will show the extent of the lesion. If the abrasion is caused by a fingernail, dirty twig, piece of chaff, edges of newspapers or contaminated objects, there is considerable danger of infection. A corneal ulcer may form and require heroic measures to save the eye. A clean abrasion may be treated by the instillation of a mydriatic with an ointment and closing the eye with a dressing until the area fails to stain with fluorescein. The dressing should be changed every twenty-four hours until healing is assured. If an infected ulcer should develop, the eye should be left open and treated with atropine solution, hot applications and antiseptics.

Contusions of the Eyeball

Contusions of the eyeball should be treated with great respect because of the complications that may arise. It is possible for dangerous hemorrhages to occur, and practically all cases exhibit some degree of traumatic iritis. Secondary glaucoma, cataract formation, detachment of the retina and other complications may characterize the damaged eye. It is not uncommon for total blindness and even enucleation to follow

Allergic conjunctivitis may be caused by pollen, cosmetics, protein foods and bacterial toxins, according to Wood. Vaso motor ... is observed in lymphoid hyperplasia and improvement may follow antihistamine. Radiation is not advocated because of the danger of cataract formation. A weak solution of sodium carbonate may give temporary relief. The cause should be discovered and eliminated if possible.

LESIONS OF THE CORNEA

Interstitial keratitis usually appears in childhood° and should have vigorous local treatment with atropine and hot fomentations. It is conceded by most syphilologists and ophthalmologists that antisyphilitic treatment should be guarded and mercury injections are safer if the vision is to be preserved. It is possible to follow mercury with a course of arsenicals after resistance to the spirochete has reached such a point that the infection will not be temporarily activated.

ful and require the same general treatment. As in most acute infections, it is often wise in the beginning to use cool applications and bland antiseptic ointments in an effort to abort the process. If the condition progresses, it is wise to use hot fomentations followed by incision, if drainage does not occur spontaneously. A vigorous effort should be made to improve the general health of the patient by means of proper rest, hygiene, food, vitamins and autogenous vaccines.

Chronic blepharitis is one of the most resistant lid infections with which the ophthalmologist has to contend. It is characterized by raw, scaly, mildly ulcerated lid margins which have a tendency to bleed when the scales are removed. The condition is often helped by removal of the scales with peroxide of hydrogen or alcohol, followed by the application of 3 per cent iodine. A mild astringent collyrium, such as ¼ per cent zinc sulfate solution, should be used at home. Mercurial ointments should be avoided immediately after the use of iodine. Vitamin A and D ointment is efficacious in the hands of some clinicians and all efforts should be made to improve the general condition of the patient.

CONJUNCTIVITIS

The common types of conjunctivitis vary according to the geographic location. It is possible that trachoma is the dominant type in certain areas in the southwest, whereas "agricultural conjunctivitis," as described by Gifford and Patton,[1] may feature certain areas in the middle west. Mild forms of staphylococcic and pneumococcic conjunctivitis are common in the eastern states.

The successful treatment of *trachoma* with sulfanilamide was verified by Gradle[2] and his co-workers in Illinois in 1939 and corroborated by Thygeson,[3] who advocated substantial doses in the earlier stages of the disease. It has been observed that smaller doses over a longer period of time are of considerable help in old cases. Great caution should be observed in the administration of the drug because serious and sometimes fatal complications may result from alteration of the blood picture.

Inclusion blennorrhea, which may be confused with gonor-

layers and destroys the function of the rods and cones after a period of time. The condition may be relieved by diathermy operations as advocated by Gradle[12] and Walker.[13] Operations for retinal detachment are not ideal but with continuous improvement in technic considerable relief is given many hopeless cases.

Traumatic detachments of the retina in young individuals usually respond better to surgery than those occurring in older persons. The location and correction of the retinal tear with a diathermy needle has great influence on the final outcome. A separation of the retina may occur at any age and be the result of a most innocuous cause. The condition has been observed after a sneeze, pat on the back or sudden strain. There is usually a weakness or disease of the retina which permits the detachment, and operation is the only hope for restoration of sight.

VITAMINS IN OPHTHALMOLOGY

The role of vitamins in the treatment of eye diseases is disputed but it is conceded by most ophthalmologists that all of the vitamins are needed by the eye and are usually included in well balanced diets. Massive doses of *Vitamin A* cause improvement of such symptoms as photophobia and color appreciation. Congenital color blindness is not improved by any of the vitamins. *Vitamin B* and its fractions are valuable in the treatment of toxic amblyopia and affections of the cornea caused by deficiency states. Preoperative administration of *vitamin C* lessens the possibility of hemorrhage during and after surgical interference. It has been found valuable in cataract and glaucoma surgery at the New York Eye and Ear Infirmary.[14] Numerous investigations have shown that vitamins are important in many eye diseases but considerable work is necessary to evaluate their complete worth.

STRABISMUS

The study of strabismus during the past few years has been greatly aided by the development of new instruments to test the fusion faculty and stimulate the eyes with exercises. Occlusion of the dominant eye and orthoptic exercises may not

Keratitis with acne rosacea is improved by riboflavin, according to Johnson and Eckhardt.[10] Other forms of keratitis show improvement with the use of vitamin B complex.

Dendritic keratitis is caused by a filtrable virus and best treated by curettage and the application of tincture of iodine with local anesthesia, according to Gunderson.[11] The cornea is usually insensible to light touch, the lesion resembles an arborization beneath the epithelium. Vitamin A ointment and atropine are useful in the treatment.

Herpes zoster ophthalmicus may cause glaucoma or iritis if the cornea is involved. Considerable skill and judgment are necessary when such complications arise. The eye should be treated with normal saline irrigations, bland ointments and mild antiseptic solutions. The use of mydriatics should be guarded. Foreign protein therapy is advocated by some ophthalmologists.

CATARACT

The causes of cataract formation are still under discussion and no appreciable advance has been made in the medical treatment for lens opacities. It is observed that patients suffering from diabetes or nephritis usually develop cataractous changes. The administration of reducing drugs such as dinitrophenol and the prolonged inhalation of certain vapors may cause cataracts. It is possible that the elimination of certain foci of infection and the correction of systemic disease may arrest the development of lens changes. Most ophthalmic surgeons insist on thorough physical and chemical studies before an operation is performed.

The choice of operations for cataract depends on the indications presented by the patient. In many cases the intracapsular method may be used but there are definite contraindications such as high myopia, prominent eyeballs and increased intraocular tension. In complicated cases it is often wise to perform the operation in two stages with capsulotomy.

DETACHMENT OF THE RETINA

The retina may become separated from the choroid by trauma or disease. An albuminous fluid lies between the two

The object in the *treatment* of squint or cross-eyes is to make the two eyes work together as a single unit. Normal individuals are able to compose the separate images of the two eyes into a single mental picture. They are able to appreciate distance and depth. The cross-eyed person cannot fuse the two mental images and has poor judgment of distance. A child usually develops the faculty of fusing the two images fairly early in life. Most authorities agree that fusion develops before the age of six or seven and rarely after that age. It is often defective if developed later in life. A test for fusion should be included in the first examination of the child, which should be performed before the ages of five or six.

In some instances, it is wise to straighten the eyes by means of *surgery* at an early date. In others, if an operation is indicated, it is wise to wait until after the age of seven. Surgery is never considered until every effort is made to correct the squint by glasses, exercises or other treatment. If *glasses* are needed, they should be worn for several months. *Exercises* should be prescribed and a patch worn over one eye if necessary. If all nonsurgical treatment is exhausted and it becomes necessary to operate, the parents should select an eye physician who has had adequate experience in eye surgery. The operation itself is not a dangerous one but requires considerable skill. Small children usually require general anesthesia but some have been operated on as young as five or six under local anesthesia. It is much better to operate under local anesthesia, whenever possible. Operations to straighten cross-eyes are almost always successful.

READING PROBLEMS:

Good vision and muscular coordination are necessary for rapid assimilation of printed matter. Adequate light, proper environment, ability to concentrate, and good mental and physical health are needed for reading. If the above factors are favorable, there is hope that, by proper correction of refractive errors and orthoptic training, the patient may become an efficient reader, provided good remedial treatment is available. The mechanics of reading should be directed by a trained technician familiar with the various psychic and

cure strabismus but a better interpretation of the condition is available for the eye surgeon.

Strabismus may be hereditary, psychic or caused by the lack of fusion. Approximately 50 per cent of the cases may be helped or cured with properly fitted glasses and orthoptic exercises. By first grade fusion is meant the ability to superimpose the image of the right eye with that of the left eye and obtain a single mental picture. Second grade fusion is superimposition with some perspective, or the ability to fuse the two images and appreciate where the objects are located in space. Third grade fusion is instantaneous appreciation of perspective or *true stereoscopic vision*.

True stereoscopic vision is ideal and is the goal we all seek in the treatment of cross-eyes. It is most important in aviation, motoring, art, architecture, sports, and vocations requiring precision. Children with muscle imbalance and fusion difficulty usually suffer from headaches, eyestrain and inability to judge distances. The trouble may not be discovered until a thorough examination is performed by an eye physician. Corrective lenses and exercises may help the child so much that glasses may be discarded after a time.

Most authorities agree that *every child should be examined by a competent eye physician before the school age*. Such an examination may indicate what is to be expected of the child in school and whether there is any tendency for the eyes to cross or become strained. The routine examination usually includes:[15]

1. An accurate estimation of the vision of each eye separately and together.
2. Muscle testing to see whether there is any tendency for the eyes to cross.
3. Stereoscopic tests to determine the degree of fusion of the images of the two eyes.
4. Examination of the eyes to eliminate granulated eyelids, tearing, scars and other conditions.
5. Measuring the eyes after using drops to relax the pupils.
6. Examination of the interior of the eye to see that no disease is present.
7. Prescription of correct glasses if necessary.
8. Exercises if indicated.

The object in the *treatment* of squint or cross-eyes is to make the two eyes work together as a single unit. Normal individuals are able to compose the separate images of the two eyes into a single mental picture. They are able to appreciate distance and depth. The cross-eyed person cannot fuse the two mental images and has poor judgment of distance. A child usually develops the faculty of fusing the two images fairly early in life. Most authorities agree that fusion develops before the age of six or seven and rarely after that age. It is often defective if developed later in life. A test for fusion should be included in the first examination of the child, which should be performed before the ages of five or six.

In some instances, it is wise to straighten the eyes by means of *surgery* at an early date. In others, if an operation is indicated, it is wise to wait until after the age of seven. Surgery is never considered until every effort is made to correct the squint by glasses. exercises or other treatment. If *glasses* are needed, they should be worn for several months. *Exercises* should be prescribed and a patch worn over one eye if necessary. If all nonsurgical treatment is exhausted and it becomes necessary to operate, the parents should select an eye physician who has had adequate experience in eye surgery. The operation itself is not a dangerous one but requires considerable skill. Small children usually require general anesthesia but some have been operated on as young as five or six under local anesthesia. It is much better to operate under local anesthesia, whenever possible. Operations to straighten cross-eyes are almost always successful.

READING PROBLEMS[16]

Good vision and muscular coordination are necessary for rapid assimilation of printed matter. Adequate light, proper environment. ability to concentrate, and good mental and physical health are needed for reading. If the above factors are favorable, there is hope that. by proper correction of refractive errors and orthoptic training. the patient may become an efficient reader. provided good remedial treatment is available. The mechanics of reading should be directed by a trained technician familiar with the various psychic and

cure strabismus but a better interpretation of the condition is available for the eye surgeon.

Strabismus may be hereditary, psychic or caused by the lack of fusion. Approximately 50 per cent of the cases may be helped or cured with properly fitted glasses and orthoptic exercises. By first grade fusion is meant the ability to super-impose the image of the right eye with that of the left eye and obtain a single mental picture. Second grade fusion is super-imposition with some perspective, or the ability to fuse the two images and appreciate where the objects are located in space. Third grade fusion is instantaneous appreciation of per-spective or *true stereoscopic vision.*

True stereoscopic vision is ideal and is the goal we all seek in the treatment of cross-eyes. It is most important in aviation, motoring, art, architecture, sports, and vocations requiring precision. Children with muscle imbalance and fusion diffi-culty usually suffer from headaches, eyestrain and inability to judge distances. The trouble may not be discovered until a thorough examination is performed by an eye physician. Cor-rective lenses and exercises may help the child so much that glasses may be discarded after a time.

Most authorities agree that *every child should be examined by a competent eye physician before the school age.* Such an examination may indicate what is to be expected of the child in school and whether there is any tendency for the eyes to cross or become strained. The routine examination usually includes:[15]

1. An accurate estimation of the vision of each eye separately and together.
2. Muscle testing to see whether there is any tendency for the eyes to cross.
3. Stereoscopic tests to determine the degree of fusion of the images of the two eyes.
4. Examination of the eyes to eliminate granulated eyelids, tearing, scars and other conditions.
5. Measuring the eyes after using drops to relax the pupils.
6. Examination of the interior of the eye to see that no dis-ease is present.
7. Prescription of correct glasses if necessary.
8. Exercises if indicated.

The object in the *treatment* of squint or cross-eyes is to make the two eyes work together as a single unit. Normal individuals are able to compose the separate images of the two eyes into a single mental picture. They are able to appreciate distance and depth. The cross-eyed person cannot fuse the two mental images and has poor judgment of distance. A child usually develops the faculty of fusing the two images fairly early in life. Most authorities agree that fusion develops before the age of six or seven and rarely after that age. It is often defective if developed later in life. A test for fusion should be included in the first examination of the child, which should be performed before the ages of five or six.

In some instances, it is wise to straighten the eyes by means of *surgery* at an early date. In others, if an operation is indicated, it is wise to wait until after the age of seven. Surgery is never considered until every effort is made to correct the squint by glasses, exercises or other treatment. If *glasses* are needed, they should be worn for several months. *Exercises* should be prescribed and a patch worn over one eye if necessary. If all nonsurgical treatment is exhausted and it becomes necessary to operate, the parents should select an eye physician who has had adequate experience in eye surgery. The operation itself is not a dangerous one but requires considerable skill. Small children usually require general anesthesia but some have been operated on as young as five or six under local anesthesia. It is much better to operate under local anesthesia, whenever possible. Operations to straighten cross-eyes are almost always successful.

READING PROBLEMS[16]

Good vision and muscular coordination are necessary for rapid assimilation of printed matter. Adequate light, proper environment, ability to concentrate, and good mental and physical health are needed for reading. If the above factors are favorable, there is hope that, by proper correction of refractive errors and orthoptic training, the patient may become an efficient reader, provided good remedial treatment is available. The mechanics of reading should be directed by a trained technician familiar with the various psychic and

mental phases of reading. If the ophthalmologist has given the patient the best glasses possible and has increased the amplitude of fusion to allow for good reading, he should be content to have remedial training directed by one more expert in that field. It is often necessary for the ophthalmologist to continue observations and exercises while remedial training is in progress, and it is most important for him to cooperate until results are attained.

Comparatively few people have normal vision in every detail. A person may be able to see perfectly in the distance with both eyes but less than normal when using each eye separately. Various *errors of refraction* influence visual acuity for both distance and near. If the errors of refraction are great enough and are not corrected properly, the patient's reading progress is impeded. Proper attention should be devoted to possible size differences of the retinal images and the condition of the intrinsic and extrinsic ocular muscles.

Good muscular coordination is necessary to make an efficient reader. We often fail to appreciate that there are intrinsic as well as extrinsic ocular muscles which have to work in perfect harmony to attain good binocular single vision. A disturbance of the function of any one of these muscles may be enough to affect seriously the ability to digest printed material. Variations in the near-points of accommodation and convergence, with consequent fatigue, play important parts in the use of the two eyes together. A weakness or overaction of the medial recti muscles frequently results in asthenopic symptoms incompatible with normal reading ability.

BIBLIOGRAPHY

1. Gifford, S. and Patton, J. M.: Agricultural Conjunctivitis. Am. J. Ophth., *5*: 623, 1922.
2. Gradle, H. S.: Trachoma in United States of America. Rev. internat. du trachome, *16*: 143, 1939; Use of Sulfanilamide in Trachoma. Rev. internat. du trachome, *16*: 163, 1939.
3. Thygeson, P.: The Treatment of Trachoma with Sulfanilamide. Am. J. Ophth., *23*: 679, 1940.
4. Julianelle, L. A. and Lange, A. C.: Studies on Inclusion Blennorrhea. I. Clinical and General Observations. Am. J. Ophth., *21*: 890, 1938.
5. Bower, A. G. and Frank, W.: Treatment of Gonorrheal Ophthalmia. Am. J. Ophth., *22*: 277, 1939.
6. Fernandez, L. J. and Fernandez, R. F.: Sulfanilamide in Gonorrheal Ophthalmia. Am. J. Ophth., *21*: 763, 1938.

7. Thygeson, P.: Treatment of Staphylococcic Conjunctivitis with Staphyl-ococcus Toxoid. Arch. Ophth., *20:* 271, 1938.

8. Woods, A. C.: Clinical Problem of Allergy in Relation to Conjunc-tivitis and Iritis. Arch. Ophth., *17:* 1, 1937.

9. Payne, B. F.: Systemic Conditions and How They May Result in the Loss of Sight. Outlook for the Blind, Vol. XXXV, No. 2, April, 1941.

10. Johnson, L. V. and Eckhardt, R. E.: Rosacea Keratitis and Conditions with Vascularization of Cornea Treated with Riboflavin. Arch. Ophth., *23:* 899, 1940.

11. Gundersen, T.: Herpes Corneae with Special Reference to Its Treat-ment with Strong Solution of Iodine. Arch. Ophth., *15:* 225, 1936.

12. Gradle, H. S.: A Simple Needle for Diathermy Treatment of Retinal Detachment. Am. J. Ophth., *18:* 956, 1935.

13. Walker, C. B.: Treatment of the Flat Type of Separated Retina and of Macular Hole with Special Devices and Modifications. Am. J. Ophth., *19:* 392, 1936.

14. Payne, B. F.: Unpublished observations from Dr. Payne's clinic, New York Eye and Ear Infirmary.

15. Payne, B. F.: Cross-eyed Children. Arch. of Pediatrics, Vol. LVIII, No. 6, June, 1941.

16. Payne, B. F.: The Effect of Vision on Reading Ability. The Sight-saving Review, Vol. XI, No. 1, March, 1941.

VITAMIN A

Some Clinical Considerations[*]

JOSEPH MANDELBAUM, M.D., Med. Sc. D.[†]

THE carotenoid pigments, alpha-, beta-, and gamma-carotene and cryptoxanthin, which occur in plant life, are the sources of the vitamin A required in animal metabolism. The carotenoids occur chiefly in green vegetables, the carotenoid content roughly paralleling that of chlorophyll. Chemically, vitamin A is a methylated unsaturated aliphatic alcohol to which a beta-ionone ring is attached. Two varieties of vitamin A have been isolated: A_1, important in human economy and found in abundance in the livers of marine fish; and A_2, which has been found in the livers of fresh-water fish. The A_2 variety contains two more carbon atoms in the aliphatic chain.[25] Both are optically active, absorbing in the ultraviolet band; the absorption peak for A_1 is at 328 millimicrons, for A_2 at 345. When antimony trichloride in chloroform is added, a blue color reaction takes place. This is the *Carr-Price reaction*, the basis for the chemical determination of the vitamin content in tissues or foods.

Function of Vitamin A in Vision

Vitamin A is stored in the liver where it occurs as an ester; the next richest tissue sources of the vitamin are the choroid and retina.[74] The reason for this concentration in the eye is its participation in the *visual purple* molecule.[56] Visual purple, or rhodopsin, which is found in the rod cells of the retina, is thought to be a heavy protein with vitamin A attached as a prosthetic group.[35] There is reason to believe that visual violet, or iodopsin, the cone photosensitive pigment, also contains vitamin A.[33] It is the action of light on these photosensitive pig-

---

[*] From the Department of Ophthalmology, Long Island College of Medicine.

[†] Fellow in Ophthalmology, Long Island College of Medicine; Clinical Assistant, Brooklyn Eye and Ear Hospital.

ments which is the first step in the visual process. Visual purple has an absorption peak at 510 millimicrons; this corresponds to the brightest scotopic spectral region. The visual purple extracted from the retinas of fresh-water fish has maximum absorption at 522 millimicrons.[57] It is not known how completely A_2 may replace A_1 in mammalian economy; it does have biologic activity for rats.[28] It is conceivable that by substituting vitamin A_2 for A_1 by means of depletion and feeding experiments the spectral sensitivity curves of mammals might be altered.

Metabolism of Vitamin A

Only a few isolated facts in the metabolism of vitamin A are understood. The absorption of carotene and vitamin A from the intestines is quite variable and parallels the efficiency of fat absorption. Absorption of carotene varying from 1 and 6 per cent to 50 per cent has been reported on a fat-free diet, compared to from 50 to 90 per cent on a high fat diet.[85, 93] The secretion of bile is important for the absorption of carotene and somewhat less so for that of the vitamin. Vitamin A, being an alcohol, and therefore capable of esterification, is in general absorbed more easily. Carotene is converted to vitamin A in the liver by an enzyme called "carotenase." Thyroxin plays a role in this process, as is shown by the fact that thyroidectomized goats secrete carotene instead of vitamin A in their milk.[23] Vitamin A can be mobilized from the liver by stimulation of the splanchnic nerve or by the intravenous injection of epinephrine[97] by a mechanism apparently similar to that mobilizing sugar and plasma proteins. The ingestion of alcohol also causes a mobilization of the vitamin.[13] Ninety-five per cent of the total body supply of the vitamin is found in the liver; this store normally amounts to over 40,000 units* per 100 grams of liver and averages 121,000 units.[71] At birth there is no store of vitamin in the liver; it is a matter of years before the normal store is built up.[68]

Effect of Vitamin A Deficiency on Epithelium

The direct participation of vitamin A in the visual purple molecule explains its role in the visual process; its function in maintaining normal epithelium is not at all understood. No vitamin A was found to be present in epithelial cells by the fluorescent method recently applied.[68] Deficiency of the vitamin,

* All references to units will be in terms of the International Unit, the equivalent of .0006 mg. beta-carotene.

however, gives rise to a diffuse keratinizing metaplasia which may affect all the epithelial surfaces of the body. The typical pathologic change, as summarized by Bessey and Wolbach,[4] is an "atrophy of the epithelium concerned, reparative proliferation of basal cells, and differentiation of the new product into a stratified keratinizing epithelium. This replacement epithelium, regardless of previous functions and structure of the region, is identical in all locations and comparable in all its layers with epidermis. . . . Many of the striking gross pathological features of the deficiency in man and animals are the outcome of the accumulation of keratinized epithelial cells in the glands and their ducts and other organs."

The commonest site for the lesion in infants suffering from a deficiency is the epithelium of the respiratory tract;[5] this accounts for the frequent pneumonia deaths in these cases. Other sites commonly involved in infants are the cornea, conjunctiva, pancreas, salivary glands, renal pelves, uterus and periurethral glands. In the teeth there may be defective formation of enamel and dentin. Specific gastro-intestinal lesions, although reported in experimental animals, have not been seen in man. The plugging of ureters with keratotic cells may lead to death in anuria in animals depleted of vitamin A; urinary calculi are occasionally seen under these conditions.

Effect of Vitamin A Deficiency on the Nervous System

Mellanby[59] claims that the extensive demyelinization of sensory tracts that he has been able to produce is the essential pathology; the epithelial metaplasia he considers to be a type of epithelial neurodystrophy. The fairly rapid recovery of the epithelium when vitamin A is given is against this concept. Furthermore, other investigators have disputed his findings. Changes in the medulla which appear first in the motor tracts have also been described.[73] Degenerative changes may occur in the eighth nerve, apparently caused by exostoses in the inner auditory canal; this may lead to deafness in experimental animals. However, it has not been demonstrated that nerve deafness in man can be attributed to vitamin A deficiency.

DIAGNOSIS OF VITAMIN A DEFICIENCY

With manifest symptoms of the deficiency, such as the typical epithelial lesions or night blindness (nyctalopia) occurring in a patient whose dietary history suggests a deficiency,

no special methods are required to make the diagnosis. It is desirable, however, to make the diagnosis when the condition is less obvious, and before structural changes have occurred. Several methods have been employed to diagnose this subclinical deficiency state. Most widely used among these methods are *dark adaptation measurements*.

Dark Adaptation Measurements

The groundwork for this method was the experiments of Fridericia and Holm[25] and Tansley,[64] who showed that night blindness could be produced in experimental animals on a vitamin A deficient diet and that the reason for this was insufficient regeneration of visual purple.

Instruments.—To Jeans and Zentmire[42] goes the credit for arousing interest in this country in the problem of the detection of subclinical vitamin A deficiency. They used the Birch-Hirschfeld *Adaptometer*. Subsequently this was modified and incorporated into the *Biophotometer*,[40] the most widely used instrument in this country for the measurement of dark adaptation.

Dark adaptation is a complex physiological phenomenon which reflects the regeneration of visual purple and visual violet in the rod and cone cells.[32, 55] Certain factors must be controlled before accurate measurements can be made. These factors include the brightness and duration of the adapting light, and the retinal location, color, size and duration of the test light.[23] The Biophotometer does not adequately control all these factors; for this reason much of the work reported with it is open to question and has been criticized.[62] Some observers found no correlation between the dietary histories and the Biophotometer readings.[39, 60] In the hands of other investigators the instrument gave results consistent with the dietary histories.[8, 43, 53] A rather arbitrary criterion for normalcy was established by Jeans; this serves to increase the reported incidence of deficiency. The technic with the instrument could be improved if the later readings were emphasized rather than the first reading taken at the start of dark adaptation.[8] The instrument should be considered largely qualitative, capable of differentiating the grossly abnormal from the normal. It should be remembered that small differences recorded with it are without great significance.

Hecht and Shlaer[26] introduced an instrument which satisfies the physiologic requirements for proper dark adaptation measurements.

Among other dark adaptation instruments that have been used to determine the condition of vitamin A nutrition may be mentioned that of Feldman[24] and that of Pett.[65] Haig's instrument may be used to measure the light sensitivity of infants.[31]

Normal Variations in Light Threshold.—Hecht and Mandelbaum,[33] investigating a "normal" university population, found that the final rod light threshold values extended over a range of one log unit, or ten times. Within this range there seemed to be no correlation with the diets. Other factors which might account for individual variation within the normal range include the availability of the protein component of visual purple, the thresholds of the intermediate neurons in the retina and optic tract, and cerebral factors. Day to day variations accounted for differences as large as 0.3 log unit. Alcohol can produce a uniform elevation of cone and rod thresholds,[75] an effect similar to that of oxygen deprivation[52] and in all likelihood cerebral in location.

Variations in Light Threshold in Vitamin A Deficiency.—The effect of a vitamin A deficient diet is to bring about a rise in both the cone and rod light thresholds; the transition time between cone and rod function is not changed. The rate at which different individuals manifest depletion by a rise in light thresholds is extremely variable. An effect may be evident almost immediately, or months may elapse before it appears.[7, 34, 55, 59] The reason for the individual differences in the rate of depletion is not known; possibly a long time storage factor is involved. No significant correlation was found between the original threshold level within the normal range and the rate of depletion;[34] this confirms the impression that factors other than the store of vitamin A determine the threshold level within the normal range.

The rate of recovery from the state of depletion, as measured by dark adaptation, is also very variable. Recovery may be complete within an hour after the administration of a large dose of vitamin to a deficient subject,[51, 55, 59] but it is more often prolonged.[34] The administration or withholding of other vitamins seems to have no effect either on the course of depletion or the rate of recovery.[34, 97] It is possible that some individuals whose thresholds fall within the normal range are somewhat deficient in vitamin A and do not give the most efficient light thresholds possible. Hecht and Mandelbaum[33] found this to be true in only one case. Young and Wald[97] however, found a greater percentage demonstrating a "vitamin lability" as evidenced by an improvement in the final light threshold greater than 0.3 log unit

in extent and appearing usually within a day after the administration of a large dose of vitamin A. Their population was selected, however, because of its very poor dietary history particularly with respect to vitamin A.

Wherever poor light sensitivity is found, organic disease of the retina must be ruled out before vitamin A deficiency can be diagnosed. Among the conditions causing poor light sensitivity are retinitis pigmentosa, glaucoma, optic atrophy, chorioretinitis and congenital nyctalopia.[55]

Blood Level of Vitamin A

The chemical basis for the determination of the vitamin A level of the blood is the Carr-Price reaction, described above. The blue color which is formed is fleeting, and the early attempts to standardize a technic for the diagnosis of vitamin A deficiency by the determination of the blood content were necessarily inaccurate. With the photo-electric colorimeter[21] more accurate measurements are possible. The yellow color of a petroleum ether extract of blood plasma is first read through a violet filter; this gives the carotene content. The solvent is then evaporated to dryness, and the Carr-Price reagent is added. The density of the blue color is then measured photo-electrically, the maximum swing of the galvanometer being recorded as a measure of the reaction. The carotene component of the blue reaction is determined from the carotene content previously determined. The difference between the total blue reaction and that due to carotene gives the reaction due to vitamin A. Kimble[44] gives the normal range for carotene and vitamin A in adults as follows:

	Carotene (Mg. per 100 cc.)	Vitamin A (Units per 100 cc.)
Males	0 05–0 30	86–192
Females	0 09–0 34	64–164

The blood level of vitamin A is higher in males than in females (no sex difference in light thresholds has been observed[33]). There was no correlation between the levels of carotene and vitamin A. There was no postprandial rise either in the carotene or vitamin A level under normal circumstances; a rise to three times the previous level could be brought about by the feeding of a vitamin concentrate. Lewis, Bodansky and Haig found that the blood vitamin A is lowest in infants below the age of six months (average value: 74 units per 100 cc.) and rises gradually throughout infancy and childhood.[49]

Whether or not the blood content of vitamin A is a better test for the nutritional status than is a functional test like dark adaptation is not clear at present. A good clinical test for vitamin A should indicate whether the body stores are low or whether the utilization of the vitamin is deficient; these factors do not necessarily parallel the blood level. Thus, during a depletion diet the blood level may remain normal for some time after a single daily maintenance dose, which could not have replaced the body's stores.[50] In rats the blood content has been found to parallel the intake only up to the level of 50 units daily; above this the blood level remains constant.[48] The liver store in rats is built up when the blood level exceeds 37 units per 100 cc.; above this level there is no correlation between blood level and liver content. In man, a normal liver store is not required to maintain a normal blood level.[57]

A correlation between light sensitivity and the blood level of the vitamin has been claimed;[66] most investigators, however, failed to find it.[2, 3, 50] The most recent work shows no correlation within the normal range; with grossly abnormal cases a correlation is found.[49] In infants whose age varied from one and one-half to four months, a vitamin A-free diet brought about a reduction in the blood vitamin A level below the normal minimum value of 45 units per 100 cc.; accompanying this there was a diminution in light sensitivity. When 150 units of vitamin A daily was given subsequently, light sensitivity returned to normal while the blood vitamin level remained depressed.[6]

Conjunctival Changes in Vitamin A Deficiency

Kruse, using biomicroscopy, found very early changes in the conjunctiva which he attributes to vitamin A deficiency;[45] he found these changes to occur earlier than changes in dark adaptation. The changes he observed were diminished luster and transparency of the conjunctiva, increased vascularization, and the appearance of Bitot's spots. Improvement in all cases was achieved by the daily administration of large doses of vitamin A. However, this work has not yet been confirmed. The high incidence of Bitot's spots and other early signs of xerophthalmia which he records are certainly outside the experience of most ophthalmologists working in clinics with population groups at least as poor as those he studied.

THE OPTIMUM VITAMIN A REQUIREMENT

Since vitamin A can be stored, it is desirable that a *minimum daily intake* be established which would not only prevent the symptoms of vitamin A deficiency, but would also allow a store to be built up in the liver. So far this optimum minimum is largely conjectural, and various recommendations are made by various investigators.

Using the maintenance of normal dark adaptation as a criterion for adequate intake, Booher, Callison and Hewston[7] found that 25 to 55 units per kilogram of body weight were sufficient in adults. To allow for individual variations, they recommended 3000 units as the daily requirement for adults; 5000 units daily was recommended for pregnant women and 6000 to 8000 for growing children. However, Jeans, Blanchard and Satterthwaite[41] found that 2000 units daily were sufficient for growing children. Furthermore, Lewis and Haig[50] found that infants require only 18 to 20 units daily per kilogram of body weight in order to maintain normal dark adaptation. Infants receiving only 135 to 200 units daily, which is only one-twelfth the average normal dietary allowance, had as good dark adaptation as those receiving supplements up to 17,000 units daily. There was no difference in the rate of gain in weight or in the incidence of infections between infants receiving a normal diet and those whose vitamin A intake was cut down to one-fourth normal;[47] however, the average blood vitamin A level was reduced from 74 units per 100 cc. to 61 units during a period of two to four months.[6] It may be concluded that a large safety factor is provided in the normal infant diet which should be adequate for ample storage.

Using a visual function test, Edmund and Clemmesen[19] determined that the daily adult intake requirement was 20 to 22 units per kilogram of body weight. In cattle the minimum daily requirement in order to maintain normal light sensitivity was found to be 25 units per kilogram;[30] the same requirement also held for sheep and swine. The constant requirement per unit of body weight which has been reported for adults, infants and various mammals suggests that the dependence on body weight is the determining factor. It would follow that

infants and children require not more vitamin A than adults, but much less, and that their daily requirements could easily be fulfilled by a diet containing an adequate quantity of milk.

The need for vitamin A *during pregnancy* is probably greater than normal; 6000 units daily has been suggested as an adequate amount. The basis for this is the reported high incidence of vitamin A deficiency during pregnancy. Forty per cent of pregnant women were found to have subnormal blood vitamin.[57]

INCIDENCE OF VITAMIN A DEFICIENCY

The percentage of the population suffering from subclinical vitamin A deficiency has been variously estimated. Most surveys have been made with the Biophotometer, according to a technic which probably exaggerates the percentage reported deficient.[15, 40] In a university population, Hecht and Mandelbaum,[33] working with a more accurate adaptometer, found only one case in 110 deficient, as contrasted with Jegher's Biophotometer report of 55 medical students deficient out of 162.[43] Steven and Wald,[51] studying a population group selected for its poor diet with respect to vitamin A in Newfoundland and Labrador, where epidemics of night blindness are not uncommon, found an incidence of deficiency of only 9.7 per cent; of these cases, 3 per cent had been aware of subjective night blindness. Furthermore, by means of their "vitamin lability" technic, they included subjects whose deficiency would not have been diagnosed in an ordinary survey. It is improbable that comparable groups in this country have a higher rate of deficiency.

In analyzing the diets of wage earners and clerical workers, Stiebeling and Phipard[52] found that 25 per cent consumed less than 2000 units daily; 75 per cent less than 4500 units; and 90 per cent less than 6000. However, since the normal requirement is not actually known, the deficiency rate as judged by dietary standards cannot be accurately stated. Hunt[55] did find a significant correlation between the light threshold levels and the diet in high and low income groups of high school children; the rather small difference, however, suggests that there was not a high rate of deficiency in the low income group.

By the method of biomicroscopic examination of the conjunctiva described by Kruse.[45] much higher rates of deficiency are reported than with any other technic. In a group of 166 workers whose incomes ranged from fifty-two to ninety-five dollars per

month, grossly observed Bitot's spots were seen in 35 per cent; 45 per cent showed gross xerotic changes and 54 per cent, microscopic changes. Examination of high school children in a low income group showed that 86.6 per cent had xerotic changes.[91] These findings, however, should be confirmed by other investigators before they receive serious consideration.

VITAMIN A DEFICIENCY IN DISEASE

The classical lesion associated with vitamin A deficiency is *xerophthalmia*. This disease was not uncommon in Europe during the famines caused by the last war. It is endemic in China, where Pillat[67] made extensive investigations. In this disease the conjunctiva and cornea first become dry and lusterless. *Bitot's spots* appear on the conjunctiva: these are foamy collections of keratinized epithelial cells which can be removed with difficulty, only to reappear in the same place. Folds appear in the conjunctiva, which takes on a leathery appearance. The dryness is increased by plugging of the ducts of the lacrimal glands with keratinized epithelial cells. Finally the cornea becomes soft, opaque, ulcerated, and even perforated. Xerophthalmia is rarely seen in this country; the only recent case reports concern patients whose vitamin A metabolism was defective.

In the skin, the lesion of vitamin A deficiency has been named *phrynoderma*, or toad skin. The essential pathology is the formation or horny papules formed by the plugging of hair follicles by keratotic cells. This disease has been described extensively in Africa and Asia, but only recently in this country.[46, 96]

Diseases Interfering with Absorption of Vitamin A

The most common cause for the appearance of advanced vitamin A deficiency lesions is the faulty absorption of the vitamin. Even then xerophthalmia is rare, clinical nyctalopia or a subclinical deficiency being more common. Celiac disease, fibrosis of the biliary tract, or any other disease that interferes with the absorption of fat may cause either a mild or a severe deficiency of vitamin A. Xerophthalmia has been reported occurring in chronic ulcerative colitis;[29] the eye lesion was cured in this case by the intramuscular injection of vita-

min A. Xerophthalmia has also been described in a three-months-old infant with fibrosis of the pancreas.[28]

Where it is suspected that the absorption of vitamin A is defective, a *vitamin A absorption test* may be given.[58] This consists of the determination of the blood vitamin A level before and 3, 5, 7, 9, and 12 hours after the administration of a large dose of the vitamin (6000 units per pound of body weight has been used in infants). If the absorption is normal, a rise in the blood level occurs, which averages 130 units per 100 cc. Apart from the conditions mentioned above, poor absorption was found in malnutrition, pyelonephritis, sprue, chronic otitis media, pneumonia, congenital heart disease, and cretinism,[58] as well as in catarrhal jaundice.[10]

Cirrhosis of Liver

Abnormal dark adaptation is usually found in cases of cirrhosis of the liver. Patek and Haig[63] found a characteristic defect—a delay in the cone-rod transition time, rather than a simple elevation in the thresholds, as is found in simple vitamin A deficiency. This suggested an abnormality in the intermediate metabolism of the vitamin. The administration of large doses of the vitamin (100,000 units daily, either by mouth or intramuscularly) brought about improvement. In obstructive jaundice, on the other hand, when deficient dark adaptation occurred, it took the form of a simple elevation of the cone and rod thresholds, similar to the effect of vitamin deficiency. Here the absorption of the vitamin had been reduced because of faulty biliary secretion. In general, poor dark adaptation occurring in hepatic disease is more likely to be found in cases with liver damage as indicated by liver function tests than in patients with jaundice.[95] In patients dying with cirrhosis of the liver, the vitamin A content of the liver was found to be significantly below the normal lower limit of 40,000 units per 100 gm.[71] The ratio of vitamin A to carotene was also lowered, indicating a faulty conversion of carotene to the vitamin.

Infections

Metabolism of the vitamin is interfered with during infections. The blood levels of both carotene and vitamin A were found to diminish during fever, and to rise again spontan-

month, grossly observed Bitot's spots were seen in 35 per cent; 45 per cent showed gross xerotic changes and 54 per cent, microscopic changes. Examination of high school children in a low income group showed that 86.6 per cent had xerotic changes.[91] These findings, however, should be confirmed by other investigators before they receive serious consideration.

VITAMIN A DEFICIENCY IN DISEASE

The classical lesion associated with vitamin A deficiency is *xerophthalmia*. This disease was not uncommon in Europe during the famines caused by the last war. It is endemic in China, where Pillat[67] made extensive investigations. In this disease the conjunctiva and cornea first become dry and lusterless. *Bitot's spots* appear on the conjunctiva: these are foamy collections of keratinized epithelial cells which can be removed with difficulty, only to reappear in the same place. Folds appear in the conjunctiva, which takes on a leathery appearance. The dryness is increased by plugging of the ducts of the lacrimal glands with keratinized epithelial cells. Finally the cornea becomes soft, opaque, ulcerated, and even perforated. Xerophthalmia is rarely seen in this country; the only recent case reports concern patients whose vitamin A metabolism was defective.

In the skin, the lesion of vitamin A deficiency has been named *phrynoderma*, or toad skin. The essential pathology is the formation or horny papules formed by the plugging of hair follicles by keratotic cells. This disease has been described extensively in Africa and Asia, but only recently in this country.[46, 96]

Diseases Interfering with Absorption of Vitamin A

The most common cause for the appearance of advanced vitamin A deficiency lesions is the faulty absorption of the vitamin. Even then xerophthalmia is rare, clinical nyctalopia or a subclinical deficiency being more common. Celiac disease, fibrosis of the biliary tract, or any other disease that interferes with the absorption of fat may cause either a mild or a severe deficiency of vitamin A. Xerophthalmia has been reported occurring in chronic ulcerative colitis;[29] the eye lesion was cured in this case by the intramuscular injection of vita-

Urinary Lithiasis

In urinary lithiasis deficient light sensitivity was observed by Ezickson and Feldman[22] and by Patek and Haig.[64] Reviewing forty-one cases of urinary lithiasis occurring in children in Syria, Brown and Brown[11] suggest that a deficiency in vitamin A might be an etiologic factor. The occasional occurrence of renal lithiasis in experimental animals depleted of vitamin A suggests a relationship; this, however, is not uniformly observed.

THERAPEUTIC CONSIDERATIONS

Under normal circumstances, where the dietary history is normal and free from economic privation or food idiosyncrasy, the use of supplementary doses of vitamin A is probably of no value whatever. It has not been shown that infants or growing children require more vitamin A than adults do; the reverse is probably true because of the direct dependence on the body weight that has been demonstrated. Since their requirements are small, infants get more than a liberal allowance from the milk in their diet. There is no evidence that the feeding of large doses of vitamin A above the normal requirement either is beneficial to the health or reduces the susceptibility to colds or other infections.

Correction of Dietary Vitamin A Deficiency

When the diet does not contain sufficient vitamin A or carotene, supplements should be given. This may occur during economic privation. Another common cause is the avoidance of fatty foods during a reducing diet. The liberal amount of carotene supplied by the vegetables of the diet under these circumstances is likely to be poorly utilized, for the absorption of carotene is low with a low fat diet. Where a low fat diet is specifically prescribed, as is often the case in chronic cholecystitis and other diseases of the gastro-intestinal system as well as for the purpose of reducing, supplementary vitamin A should be given.

When *mineral oil* is regularly taken the absorption of carotene may be grossly reduced. It has been shown that 15 cc. of mineral oil can remove all the carotene from an ordinary meal, and that 100 cc. can remove quantitatively over 400,000

eously after the subsiding of the fever, without the administration of the vitamin.[56] Despite the fall in the blood vitamin A level during fever, the light threshold was usually found to be normal.[49] No dark adaptation abnormalities were found in a group of children with pneumonia, rheumatic fever, or other acute and chronic infections.[51] On the other hand, Biophotometer studies of a group of tuberculosis patients showed 53 per cent to have poor light sensitivity as compared to 6 and 11 per cent in two control groups.[27] In people dying of acute or chronic infections, the vitamin A content of the liver was reduced only in those cases which showed liver disease.[71]

Thyroid Disease

In thyrotoxicosis the vitamin A content of the blood may drop even to zero;[90] this is attributed to a physiological antagonism between thyroxin and vitamin A. Poor light sensitivity is commonly found in patients with thyrotoxicosis.[94] In hypothyroidism, too, diminished light sensitivity is found. This is presumably due to the lack of thyroxin which is required for the conversion of carotene into vitamin A.[23] and is consistent with the high carotenemia found in hypothyroidism.

Patek and Haig[64] found that the administration of thyroid extract or dinitrophenol to patients with chronic diseases who had poor dark adaptation resulted in a restoration of normal dark adaptation curves. The same effects were produced as could be achieved with large doses of vitamin A; improvement in dark adaptation, however, was accompanied by a fall in the blood vitamin A level. This suggests that thyroxin increases the utilization of the vitamin; and that at least in certain conditions utilization may be reciprocal to the blood content. It shows why the blood level and the dark adaptation measurements need not be correlated.

Diabetes Mellitus

In diabetes mellitus high blood carotene levels are obtained;[53] the vitamin A level is low. Apparently the conversion of carotene to vitamin A is interfered with. Poor light sensitivity has been observed in diabetes;[9] this was not improved by the administration of large doses of carotene but was improved with vitamin A.

Urinary Lithiasis

In urinary lithiasis deficient light sensitivity was observed by Ezickson and Feldman[22] and by Patek and Haig.[64] Reviewing forty-one cases of urinary lithiasis occurring in children in Syria, Brown and Brown[11] suggest that a deficiency in vitamin A might be an etiologic factor. The occasional occurrence of renal lithiasis in experimental animals depleted of vitamin A suggests a relationship; this, however, is not uniformly observed.

THERAPEUTIC CONSIDERATIONS

Under normal circumstances, where the dietary history is normal and free from economic privation or food idiosyncrasy, the use of supplementary doses of vitamin A is probably of no value whatever. It has not been shown that infants or growing children require more vitamin A than adults do; the reverse is probably true because of the direct dependence on the body weight that has been demonstrated. Since their requirements are small, infants get more than a liberal allowance from the milk in their diet. There is no evidence that the feeding of large doses of vitamin A above the normal requirement either is beneficial to the health or reduces the susceptibility to colds or other infections.

Correction of Dietary Vitamin A Deficiency

When the diet does not contain sufficient vitamin A or carotene, supplements should be given. This may occur during economic privation. Another common cause is the avoidance of fatty foods during a reducing diet. The liberal amount of carotene supplied by the vegetables of the diet under these circumstances is likely to be poorly utilized, for the absorption of carotene is low with a low fat diet. Where a low fat diet is specifically prescribed, as is often the case in chronic cholecystitis and other diseases of the gastro-intestinal system as well as for the purpose of reducing, supplementary vitamin A should be given.

When *mineral oil* is regularly taken the absorption of carotene may be grossly reduced. It has been shown that 15 cc. of mineral oil can remove all the carotene from an ordinary meal, and that 100 cc. can remove quantitatively over 400,000

units of carotene from the intestines.[17] The absorption of vitamin A, on the other hand, is not materially reduced by the presence of mineral oil. It has been suggested, therefore, that mineral oil be fortified with vitamin A in sufficient quantity to compensate for the loss of carotene.

During pregnancy a relative deficiency in vitamin A may be caused by the greater requirement. Supplementary doses of vitamin A may be given in order to bring the daily allowance up to the suggested 6000 units. That the need for this supplementary dosage is fairly widespread is suggested by an analysis of the diets of pregnant women, 62 per cent of whom consumed less than 6000 units daily.[92]

Metabolic Disturbances

In the metabolic diseases discussed in the previous section, vitamin A may frequently be given with benefit. It is particularly indicated in those diseases where there is faulty intestinal absorption, such as in *chronic ulcerative colitis, celiac disease*, and diseases of the *biliary tract* and *pancreas*. Here massive doses (100,000 to 200,000 units daily) may be given in order to compensate for the poor absorption. If this method of administration is successful, normal light thresholds and normal blood vitamin A levels should be restored. Carotene, less easily absorbed than vitamin A, should not be given.

Other methods than oral administration may be used. *Intramuscular injection* of vitamin A suspended in peanut oil has proved to be satisfactory. *Topical application* of the vitamin to the skin may be successful. (That vitamin A can be absorbed through the intact skin is generally conceded.[20] Mackie and Eddy[34] found a rise in the blood vitamin A level following the application of cod liver oil to the skin. During experimental dietary depletion topical application of an ointment containing vitamin A suspended in lanolin prevented the appearance of impaired light sensitivity; furthermore, in subjects who had been depleted of vitamin A and who continued on a deficient diet the topical application of the vitamin cream brought about an improvement in light sensitivity.[56])

In *cirrhosis of the liver* it is reasonable to give large doses of vitamin A because of the poor utilization of the vitamin as is demonstrated by dark adaptation measurements. Here again

carotene is of less value than vitamin A because of the poor conversion into vitamin A. In *diabetes mellitus* moderate doses of vitamin A may be given to substitute for the carotene in the diet which is not converted into vitamin A; 3000 units daily are probably sufficient. For similar reasons maintenance doses of vitamin A may be given in hypothyroidism.

Specific Therapy

In all of the diseases mentioned above vitamin A is given not as a cure for the disease, but in order to make up for a deficiency caused by the disease. In other diseases vitamin A has been recommended as specific therapy. In *hyperthyroidism*[78] large doses of vitamin A have been given because of the apparent physiological antagonism between thyroxin and vitamin A; the merit of this theory needs further substantiation before it can be generally recommended. Favorable results have been reported following the use of vitamin A in *peptic ulcer*[76] and in *nephrosis*;[12] these results, too, require confirmation. In *urinary lithiasis* the recommended use of vitamin A has failed to improve the clinical picture. Nevertheless where a deficiency exists in vitamin A metabolism, as is frequently indicated in this disease by dark adaptation measurements, vitamin A may be given to combat the systemic deficiency whether or not the local lesion is improved. Finally, vitamin A therapy has been suggested for a wide variety of conditions from *atrophic rhinitis* to *senile vaginitis*;[77] confirmation of the value of vitamin therapy in these conditions has not yet appeared.

Diseases of the Eye

In ophthalmologic practice, vitamin A has been suggested for many conditions; the association of xerophthalmia and night blindness with vitamin A deficiency has made ophthalmologists very conscious of the existence of the vitamin. In *xerophthalmia*, where vitamin A is the specific treatment, large doses should be given systemically together with the local application of the vitamin either as cod liver oil or in an ointment. Where *night blindness* is the presenting symptom and there is no organic eye disease to account for it, vitamin A deficiency is the most likely diagnosis. Treatment

with large doses of vitamin A (25,000–50,000 units daily) may bring about recovery; the length of time required for recovery may be days or months, depending on the degree of vitamin depletion and certain individual factors not yet understood. Where there is no obvious dietary history of vitamin A deficiency, the patient should be carefully checked for the presence of a metabolic disease which interferes with either the absorption or utilization of vitamin A. It might be mentioned here that, in a normal person whose daily vitamin A intake is adequate, the feeding of large doses of vitamin A will not improve dark adaptation.

Vitamin A is often prescribed in *retinitis pigmentosa*, despite the fact that there is no evidence that a vitamin deficiency plays a role in the pathogenesis of the disease. Certain other diseases of the eye, however, may be related to vitamin A deficiency. In *follicular conjunctivitis* a correlation was found between dietary vitamin A deficiency and the incidence and severity of the disease; recovery followed the oral administration of liberal amounts of vitamin A.[75] Redding[70] attributes the general decline in the incidence of *phlyctenular disease* which has taken place during the last generation to the general increase in the consumption of foods containing vitamin A and carotene. This is in conformity with the prevailing practice of prescribing liberal amounts of vitamin A in phlyctenular disease. Vitamin A is also often prescribed, with but dubious justification, in cases of *progressive myopia* and in *keratoconus;* the latter condition has been produced in rats on a vitamin A deficient diet.[61] It has been claimed, too, that asthenopic symptoms occurring in patients with diminished light sensitivity were relieved by the administration of vitamin A;[14] this requires confirmation.

The *local application* of cod liver oil or ointments containing vitamin A into the conjunctival sac has been recommended for many conditions. It has been used successfully in children who had xerophthalmia following gastro-enteritis and other diseases.[71] Its local use in xerophthalmia, corneal ulcers, phlyctenular keratitis, superficial punctate keratitis, blepharitis, and other diseases of the eye was summarized by de Grosz.[18]

Dermatologic Diseases

Finally, in dermatologic practice vitamin A is the specific treatment in *phrynoderma*.[96] The diminished light sensitivity which also occurs in this disease as another manifestation of the vitamin A deficiency will also respond to the vitamin A therapy. Healing of the skin lesion is relatively slow, two to four months being required with the use of massive daily doses of vitamin A (100,000 to 300,000 units daily).[46] It is probable that many other descriptive dermatologic terms such as *keratosis pilaris, lichen pilaris, icthyosis follicularis* and others will become recognized as part of the general picture of phrynoderma and amenable to treatment with vitamin A.[46] Since vitamin A can be absorbed through the skin it is possible that local application of the vitamin suspended in lanolin might be efficacious in the treatment of this disease. Because of the local concentration of the vitamin made possible by this method, it is conceivable that more rapid cures may be achieved by local application of vitamin preparations than by the systemic administration. Apart from the use of vitamin A in the specific skin lesion caused by a deficiency, the local use of the vitamin has been reported to accelerate epithelialization in burns and chronic ulcers.[1, 20, 73]

BIBLIOGRAPHY

1. Baker, W. B. and Vonachen, H. A.: Provitamin A ointment in the treatment of burns. Indust. Med., *6:* 584, 1937. 2. Baum, W. S. and McCoord, A. B.: Visual adaptation as tested with the Biophotometer and the vitamin A content of blood. J. Pediat., *14:* 110, 1939. 3. Baum, W. S. and McCoord, A. B.: Relationship between Biophotometer tests and the vitamin A content of blood of children. J. Pediat., *16:* 409, 1940. 4. Bessey, O. A. and Wolbach, S. B.: Vitamin A; physiology and pathology. J.A.M.A., *110:* 2072, 1938. 5. Blackfan, K. D. and Wolbach, S. B.: Vitamin A deficiency in infants. J. Pediat., *3:* 679, 1933. 6. Bodansky, O., Lewis, J. M. and Haig, C.: The comparative value of the blood plasma vitamin A concentration and the dark adaptation as a criterion of vitamin A deficiency. Science, *94:* 370, 1941. 7. Booher, L. E., Callison, E. C. and Hewston, E. M.: An experimental determination of the minimum vitamin A requirements of normal adults. J. Nutrition, *17:* 317, 1939. 8. Booher, L. E. and Williams, D. E.: A study of the Biophotometer as a means of measuring the vitamin A status of human adults. J. Nutrition., *16:* 343, 1938. 9. Brazer, J. G. and Curtis, A. C.: Vitamin A deficiency in diabetes mellitus. Arch. Int. Med., *65:* 90, 1940. 10. Breese, B. B. and McCoord, A. B.: Vitamin A absorption in catarrhal jaundice. J. Pediat., *16:* 139, 1940. 11. Brown, R. K. and Brown,

E. C.: Urinary stones: a study of their etiology in small children in Syria. Surgery, *9:* 415, 1941. **12.** Caldwell, G. W.: Treatment of nephrosis with vitamin A and unsaturated fatty acid therapy. Arch. Pediat., *18:* 247, 1941. **13.** Clausen, S. W. *et al.*: Effect of alcohol on vitamin A content of blood in human subjects. Science, *93:* 21, 1941. **14.** Cordes, F. C. and Harrington, D. O.: Asthenopia due to vitamin A deficiency. Am. J. Ophth., *22:* 1343, 1939. **15.** Corlette, M. B. and Youmans, J. B.: Photometric studies of visual adaptation in relation to mild vitamin A deficiency in adults. Am. J. Med. Sci., *195:* 54, 1938. **16.** Covell, W. P.: Pathological changes in the peripheral auditory mechanism due to avitaminosis. Laryngoscope, *50:* 632, 1940. **17.** Curtis, A. C. and Horton, P. B.: Utilization of vitamin A added to mineral oil. Am. J. Med. Sci., *200:* 102, 1940. **18.** deGrosz, S.: Local use of vitamin A preparations in ophthalmic practice. Arch. Ophth., *22:* 727, 1939. **19.** Edmund, C. and Clemmesen, S.: On deficiency of vitamin A and visual adaptation. Oxford Univ. Press, London, 1937. **20.** Eller, J. J. and Wolff, S.: Hormones and vitamins in cosmetics. J.A.M.A., *114:* 1864 and 2002, 1940. **21.** Evelyn, K. A.: A stabilized photoelectric colorimeter with light filters. J. Biol. Chem., *115:* 63, 1936. **22.** Ezickson, W. and Feldman, J. B.: Signs of vitamin A deficiency in the eye correlated with urinary lithiasis. J.A.M.A., *109:* 1706, 1937. **23.** Fasold, H. and Heidemann, E. K.: Ueber die Gelbfärbung der Milch thyreopriver Ziegen. Z. ges. exp. Med., *92:* 53, 1934. **24.** Feldman, J. B.: Instrument for determining course of dark adaptation and for measuring light threshold. Arch. Ophth., *12:* 81, 1934. **25.** Fridericia, L. S. and Holm, E.: Experimental contribution to the study of the relation between night blindness and malnutrition. Am. J. Physiol., *73:* 63, 1925. **26.** Gamble, R. C.: Keratomalacia and cystic fibrosis of the pancreas. Am. J. Ophth., *23:* 539, 1940. **27.** Getz, H. R., Hildebrand, G. B. and Finn, M.: Vitamin A deficiency in normal and tuberculous persons. J.A.M.A., *112:* 1308, 1939. **28.** Gillam, A. E. *et al.*: On the occurrence and constitution of the 693 millimicron chromagen (Vitamin A_2?) of fish liver oils. Biochem. J., *32:* 405, 1938. **29.** Goldberg, H. K. and Schlivek, K.: Necrosis of cornea due to vitamin A deficiency. Arch. Ophth., *25:* 122, 1941. **30.** Guilbert, H. R. and Hart, G. H.: Minimum vitamin A requirement with particular reference to cattle. J. Nutrition. *10:* 409, 1935. **31.** Haig, C. and Lewis, J. M.: A simple method of measuring brightness threshold of dark adapted eye at all ages. Proc. Soc. Exp. Biol. & Med., *41:* 415, 1939. **32.** Hecht, S.: Rods, cones and the chemical basis of vision. Physiol. Rev., *17:* 239, 1937. **33.** Hecht, S. and Mandelbaum, J.: The relation between vitamin A and dark adaptation. J.A.M.A., *112:* 1910, 1939. **34.** Hecht, S. and Mandelbaum, J.: Dark adaptation and experimental human vitamin A deficiency. Am. J. Physiol., *130:* 651, 1940. **35.** Hecht, S. and Pickels, E. G.: The sedimentation constant of visual purple. Proc. Nat. Acad. Sci., *24:* 172, 1938. **36.** Hecht, S. and Shlaer, S.: An adaptometer for measuring human dark adaptation. J. Optical Soc. Amer., *28:* 269, 1938. **37.** Hirst, J. C. and Shoemaker, R. E.: Vitamin A in pregnancy: comparison of dark adaptation and serum tests. Am. J. Obst. and Gyn., *42:* 401, 1941. **38.** Hunt, E. P.: Dark adaptation of high school children at different income levels. Milbank Memorial Fund Quarterly, *19:* 252, 1941. **39.** Isaacs, B. L., Jung, F. T. and Ivy, A. C.: Vitamin A deficiency and dark adaptation. J.A.M.A., *111:* 777, 1938. **40.** Jeans, P. C., Blanchard, E. and Zentmire, Z.: Dark adaptation and vitamin A.

J.A.M.A., 108: 451. 1937. 41. Jeans, P. C., Blanchard, E. L. and Satterthwaite, F. E.: Dark adaptation and vitamin A. J. Pediat., 18: 170, 1941. 42. Jeans, P. C. and Zentmire, Z.: A clinical method for determining moderate degrees of vitamin A deficiency. J.A.M.A., 102: 892, 1934. 43. Jeghers, H.: Degree of prevalence of vitamin A deficiency in adults. J.A.M.A., 109: 756, 1937. 44. Kimble, M. S.: The photoelectric determination of vitamin A and carotene in human plasma. J. Lab. & Clin. Med., 24: 1055, 1939. 45. Krase, H. D.: Ocular manifestations of avitaminosis A with special consideration of detection of early changes in biomicroscopy. Milbank Memorial Fund Quart., 19: 207, 1941. 46. Lehman, E. and Rapaport, H. G.: Cutaneous manifestation of vitamin A deficiency in children. J.A.M.A., 114: 386, 1940. 47. Lewis, J. M. and Barenberg, L. H.: The relationship of vitamin A to the health of infants. J.A.M.A., 116: 1338, 1938. 48. Lewis, J. M., Bodansky, O., Falk, K. G. and McGuire, G.: Relationship of vitamin A blood level in the rat to vitamin A intake and liver storage. Proc. Soc. Exp. Biol. & Med., 46: 248, 1941. 49. Lewis, J. M., Bodansky, O. and Haig, C.: Evaluation of vitamin A blood level as an index of vitamin A deficiency in infants and children. Am. J. Dis. Child. (in press). 50. Lewis, J. M. and Haig, C.: Vitamin A requirements in infancy as determined by dark adaptation. J. Pediat., 15: 812, 1940. 51. Lewis, J. M. and Haig, C.: Vitamin A status of children as determined by dark adaptation. J. Pediat., 16: 285, 1940. 52. McFarland, R. A. and Evans, J. N.: Alterations in dark adaptation under reduced oxygen tension. Am. J. Physiol., 127: 37, 1939. 53. Mack, P. B. and Sanders, A. P.: The vitamin A status of families in widely different economic levels. Am. J. Med. Sc., 199: 686, 1940. 54. Mackie, T. T. and Eddy, W. H.: The clinical value of vitamin determinations. Am. J. Digest. Dis. & Nutrition, 6: 617, 1939. 55. Mandelbaum, J.: Dark adaptation: some physiologic and clinical considerations. Arch. Ophth., 26: 203, 1941. 56. Mandelbaum, J.: The absorption of vitamin A through the human skin (in preparation). 57. May, C. D., Blackfan, K. D., McCreary, J. F. and Allen, F. H.: Chemical studies of vitamin A in infants and children. Am. J. Dis. Child., 59: 1167, 1940. 58. May, C. D. and McCreary, J. F.: The absorption of vitamin A in celiac disease. J. Pediat., 18: 200, 1941. 59. Mellanby, E.: Lesions of central and peripheral nervous systems produced in young rabbits by vitamin A deficiency and high cereal intake. Brain, 58: 141, 1935. 60. Mellanby, E.: The experimental production of deafness in young animals by diet. Laryngoscope, 49: 1090, 1939. 61. Mutch, J. R. and Richards, M. B.: Keratoconus experimentally produced in the rat by vitamin A deficiency. Brit. J. Ophth., 23: 381, 1939. 62. Palmer, C. E. and Blumberg, H.: The use of dark adaptation technique (Biophotometer) in the measurement of vitamin A deficiency. Pub. Health Reports, 52: 1403, 1937. 63. Patek, A. J. and Haig, C.: The occurrence of abnormal dark adaptation and its relation to vitamin A metabolism in patients with cirrhosis of the liver. J. Clin. Invest., 18: 609, 1939. 64. Patek, A. J. and Haig, C.: Effect of administration of thyroid extract and of dinitrophenol upon dark adaptation. Proc. Soc. Exp. Biol. & Med., 46: 180, 1941. 65. Patek, L. B.: Vitamin A deficiency: its prevalence and importance as shown by a new test. J. Lab. & Clin. Invest., 25: 149, 1939. 66. Patek, L. B. and LePage, G. A.: Vitamin A deficiency: blood analysis correlated with visual test. J. Biol. Chem., 152: 585, 1940. 67. Pillat, A.: Does keratomalacia exist in adults? Arch. Ophth., 2: 399, 1929.

68. Popper, H.: Distribution of vitamin A in the body. J. Mt. Sinai Hospital, 7: 119, 1940. 69. Puestow, C. B., Poncher, H. G. and Hammatt, H.: Vitamin oils in the treatment of burns. Surg., Gynec. & Obst., 66: 622, 1938. 70. Radzikhovskij, B. L.: Local application of cod liver oil in cases of keratomalacia. Vestnik. oftal., 16: 434, 1940. 71. Ralli, E. P., Popper, E., Paley, K. and Bauman, E.: Vitamin A and carotene content of human livers in normal and diseased subjects. Arch. Int. Med., 68: 102, 1941. 72. Redding, L. G.: Phlyctenular disease and vitamin A deficiency. Penn. Med. J., 44: 704, 1941. 73. Richards, M. B. and Irving, J. T.: Early lesions of vitamin A deficiency. J. Physiol., 94: 307, 1938. 74. Sakamato, T.: Verteilung des Vitamins A in tieriechen Geweben. J. Biochem., 32: 425, 1940. 75. Sandels, M., Cate, H. D., Wilkinson, K. P. and Graves, L. J.: Follicular conjunctivitis in school children as an expression of vitamin A deficiency. Am. J. Dis. Child., 62: 101, 1941. 76. Seelig, S. F.: The treatment of gastric ulcer with vitamin A. Guys' Hospital Reports, 90: 41, 1941. 77. Simpson, J. W. and Mason, K. E.: A new concept of senile vaginitis. Am. J. Obst. & Gyn., 32: 125, 1936. 78. Soskin, S. and Mirsky, I. A.: Medical treatment of hyperthyroidism with high fat diet. J.A.M.A., 110: 1337, 1938. 79. Steffens, L. F., Bair, H. L. and Sheard, C.: Photometric measurements on visual adaptation in normal adults on diets deficient in vitamin A. Proc. Staff Meet. Mayo Clinic, 14: 698, 1939. 80. Steininger, G., Roberts, L. J. and Brenner, S.: Vitamin A in blood of normal adults. J.A.M.A., 113: 2381, 1939. 81. Stevens, D. and Wald, G.: Vitamin A deficiency; a field study in Newfoundland and Labrador. J. Nutrition, 21: 461, 1941. 82. Stiebeling, H. K. and Phipard, E. F.: Diets of families of employed wage earners and clerical workers in cities. U. S. Dept. Agric. No. 507. U. S. Printing Office, 1939. 83. Stueck, G. H., Flaum, G. and Ralli, E. P.: Serum carotene in diabetic patients with clinical evidence of carotenemia as determined by photoelectric colorimeter. J.A.M.A., 109: 343, 1937. 84. Tansley, K.: The regeneration of visual purple: its relation to dark adaptation and night blindness. J. Physiol., 71: 442, 1931. 85. van Eekelen, M. and Pannevis, W.: Absorption of carotenoids from the human intestines. Nature, 141: 203, 1938. 86. Wald, G.: Carotenoids and the visual cycle. J. Gen. Physiol., 19: 351, 1935. 87. Wald, G.: The porphyropsin cycle. J. Gen. Physiol., 22: 775, 1937. 88. Wald, G., Jeghers, H. and Arminio, J.: An experiment in human dietary night blindness. Am. J. Physiol., 127: 732, 1938. 89. Wald, G. and Steven, D.: An experiment in human vitamin A deficiency. Am. J. Physiol., 128: 468, 1939. 90. Wendt, H.: Changes in the carotene-vitamin A economy in myxedema and cretinism. Münchner mediz. Wochenschrift, 82: 1679, 1935. 91. Wiehl, D. J. and Kruse, H. D.: Prevalence of deficiency diseases in their subclinical stage. Milbank Memorial Fund Quart., 19: 241, 1941. 92. Williams, P. F., Hark, B. and Fralin, F. G.: Nutrition study in pregnancy. Am. J. Obst. & Gyn., 40: 1, 1940. 93. Wilson, H. E. C., Das Gupta, S. M. and Ahmad, B.: Studies on the absorption of carotene and vitamin A in human subjects. Indian J. Med. Res., 24: 807, 1937. 94. Wohl, M. G. and Feldman, J. B.: Vitamin A deficiency in diseases of the thyroid. Endocrinology, 24: 389, 1939. 95. Wohl, M. G. and Freeman, J. T.: Vitamin deficiency and certain diseased states. Tran. Am. Therap. Soc., p. 80, 1940. 96. Youmans, J. B. and Corlette, M. B.: Specific dermatoses due to vitamin A deficiency. Am. J. Med. Sci., 195: 644, 1938. 97. Young, G. and Wald, G.: The mobilization of vitamin A by the sympathetic-adrenal system. Am. J. Physiol., 131: 210, 1940.

CUMULATIVE INDEX

68. Popper, H.: Distribution of vitamin A in the body. J. Mt. Sinai Hospital, 7: 119, 1940. 69. Puestow, C. B., Poncher, H. G. and Hammatt, H.: Vitamin oils in the treatment of burns. Surg., Gynec. & Obst., 66: 622, 1938. 70. Radzikhovskij, B. L.: Local application of cod liver oil in cases of keratomalacia. Vestnik. oftal., 16: 434, 1940. 71. Ralli, E. P., Popper, E., Paley, K. and Bauman, E.: Vitamin A and carotene content of human livers in normal and diseased subjects. Arch. Int. Med., 68: 102, 1941. 72. Redding, L. G.: Phlyctenular disease and vitamin A deficiency. Penn. Med. J., 44: 704, 1941. 73. Richards, M. B. and Irving, J. T.: Early lesions of vitamin A deficiency. J. Physiol., 94: 307, 1938. 74. Sakamato, T.: Verteilung des Vitamins A in tieriechen Geweben. J. Biochem., 32: 425, 1940. 75. Sandels, M., Cate, H. D., Wilkinson, K. P. and Graves, L. J.: Follicular conjunctivitis in school children as an expression of vitamin A deficiency. Am. J. Dis. Child., 62: 101, 1941. 76. Seelig, S. F.: The treatment of gastric ulcer with vitamin A. Guys' Hospital Reports, 90: 41, 1941. 77. Simpson, J. W. and Mason, K. E.: A new concept of senile vaginitis. Am. J. Obst. & Gyn., 32: 125, 1936. 78. Soskin, S. and Mirsky, I. A.: Medical treatment of hyperthyroidism with high fat diet. J.A.M.A., 110: 1337, 1938. 79. Steffens, L. F., Bair, H. L. and Sheard, C.: Photometric measurements on visual adaptation in normal adults on diets deficient in vitamin A. Proc. Staff Meet. Mayo Clinic, 14: 698, 1939. 80. Steininger, G., Roberts, L. J. and Brenner, S.: Vitamin A in blood of normal adults. J.A.M.A.. 113: 2381, 1939. 81. Stevens, D. and Wald, G.: Vitamin A deficiency; a field study in Newfoundland and Labrador. J. Nutrition, 21: 461, 1941. 82. Stiebeling, H. K. and Phipard, E. F.: Diets of families of employed wage earners and clerical workers in cities. U. S. Dept. Agric. No. 507. U. S. Printing Office, 1939. 83. Stueck, G. H., Flaum, G. and Ralli, E. P.: Serum carotene in diabetic patients with clinical evidence of carotenemia as determined by photoelectric colorimeter. J.A.M.A., 109: 343, 1937. 84. Tansley, K.: The regeneration of visual purple: its relation to dark adaptation and night blindness. J. Physiol., 71: 442, 1931. 85. van Eekelen, M. and Pannevis, W.: Absorption of carotenoids from the human intestines. Nature, 141: 203, 1938. 86. Wald, G.: Carotenoids and the visual cycle. J. Gen. Physiol., 19: 351, 1935. 87. Wald, G.: The porphyropsin cycle. J. Gen. Physiol., 22: 775, 1937. 88. Wald, G., Jeghers, H. and Arminio, J.: An experiment in human dietary night blindness. Am. J. Physiol., 127: 732, 1938. 89. Wald, G. and Steven, D.: An experiment in human vitamin A deficiency. Am. J. Physiol., 128: 468, 1939. 90. Wendt, H.: Changes in the carotene-vitamin A economy in myxedema and cretinism. Münchner mediz. Wochenschrift, 82: 1679, 1935. 91. Wiehl, D. J. and Kruse, H. D.: Prevalence of deficiency diseases in their subclinical stage. Milbank Memorial Fund Quart., 19: 241, 1941. 92. Williams, P. F., Hark, B. and Fralin, F. G.: Nutrition study in pregnancy. Am. J. Obst. & Gyn., 40: 1, 1940. 93. Wilson, H. E. C., Das Gupta, S. M. and Ahmad, B.: Studies on the absorption of carotene and vitamin A in human subjects. Indian J. Med. Res., 24: 807, 1937. 94. Wohl, M. G. and Feldman, J. B.: Vitamin A deficiency in diseases of the thyroid. Endocrinology, 24: 389, 1939. 95. Wohl, M. G. and Freeman, J. T.: Vitamin deficiency and certain diseased states. Tran. Am. Therap. Soc., p. 80, 1940. 96. Youmans, J. B. and Corlette, M. B.: Specific dermatoses due to vitamin A deficiency. Am. J. Med. Sci., 195: 644, 1938. 97. Young, G. and Wald, G.: The mobilization of vitamin A by the sympathetic-adrenal system. Am. J. Physiol., 131: 210, 1940.